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Pharmaceutical policies: effects of cap and co-payment on rational use of medicines (Review)

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[Intervention Review]

Pharmaceutical policies: effects of cap and co-payment on rational use of medicines

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ABSTRACT

Background

Growing expenditures on prescription medicines represent a major challenge to many health systems. Cap and co-payment policies are intended as an incentive to deter unnecessary or marginal utilisation, and to reduce third-party payer expenditures by shifting parts of the financial burden from insurers to patients, thus increasing their financial responsibility for prescription medicines. Direct patient payment policies include caps (maximum numbers of prescriptions or medicines that are reimbursed), fixed co-payments (patients pay a fixed amount per prescription or medicine), co-insurance (patients pay a percentage of the price), ceilings (patients pay the full price or part of the cost up to a ceiling, after which medicines are free or are available at reduced cost) and tier co-payments (differential co-payments usually assigned to generic and brand medicines). This is the first update of the original review.

Objectives

To determine the effects of cap and co-payment (cost-sharing) policies on use of medicines, healthcare utilisation, health outcomes and costs (expenditures).

Search methods

For this update, we searched the following databases and websites: The Cochrane Central Register of Controlled Trials (CENTRAL) (including the Cochrane Effective Practice and Organisation of Care (EPOC) Group Specialised Register, Cochrane Library; MEDLINE, Ovid; EMBASE, Ovid; IPSA, EBSCO; EconLit, ProQuest; Worldwide Political Science Abstracts, ProQuest; PAIS International, ProQuest; INRUD Bibliography; WHOLIS, WHO; LILACS), VHL; Global Health Library WHO; PubMed, NHL; SCOPUS; SciELO, BIREME; OpenGrey; JOLIS Library Network; OECD Library; World Bank e-Library; World Health Organization, WHO; World Bank Documents & Reports; International Clinical Trials Registry Platform (ICTRP), WHO; ClinicalTrials.gov, NIH. We searched all databases during January and February 2013, apart from SciELO, which we searched in January 2012, and ICTRP and ClinicalTrials.gov, which we searched in March 2014.

Selection criteria

We defined policies in this review as laws, rules or financial or administrative orders made by governments, non-government organisations or private insurers. We included randomised controlled trials, non-randomised controlled trials, interrupted time series studies, repeated measures studies and controlled before-after studies of cap or co-payment policies for a large jurisdiction or system of care. To be included,

a study had to include an objective measure of at least one of the following outcomes: medicine use, healthcare utilisation, health outcomes or costs (expenditures).

Data collection and analysis

Two review authors independently extracted data and assessed study limitations. We reanalysed time series data for studies with sufficient data, if appropriate analyses were not reported.

Main results

We included 32 full-text articles (17 new) reporting evaluations of 39 different interventions (one study - Newhouse 1993 - comprises five papers). We excluded from this update eight controlled before-after studies included in the previous version of this review, because they included only one site in their intervention or control groups. Five papers evaluated caps, and six evaluated a cap with co-insurance and a ceiling. Six evaluated fixed co-payment, two evaluated tiered fixed co-payment, 10 evaluated a ceiling with fixed co-payment and 10 evaluated a ceiling with co-insurance. Only one evaluation was a randomised trial. The certainty of the evidence was found to be generally low to very low.

Increasing the amount of money that people pay for medicines may reduce insurers' medicine expenditures and may reduce patients' medicine use. This may include reductions in the use of life-sustaining medicines as well as medicines that are important in treating chronic conditions and medicines for asymptomatic conditions. These types of interventions may lead to small decreases in or uncertain effects on healthcare utilisation. We found no studies that reliably reported the effects of these types of interventions on health outcomes.

Authors' conclusions

The diversity of interventions and outcomes addressed across studies and differences in settings, populations and comparisons made it difficult to summarise results across studies. Cap and co-payment polices may reduce the use of medicines and reduce medicine expenditures for health insurers. However, they may also reduce the use of life-sustaining medicines or medicines that are important in treating chronic, including symptomatic, conditions and, consequently, could increase the use of healthcare services. Fixed co-payment with a ceiling and tiered fixed co-payment may be less likely to reduce the use of essential medicines or to increase the use of healthcare services.

PLAIN LANGUAGE SUMMARY

The effect of direct payment policies on people's use of medicines

Researchers at The Cochrane Collaboration conducted the first update of the original review of the effects of different policies determining how much people should pay for their medicines. Between 2011 and 2013, they searched for all relevant studies and found 32 studies. Their findings are summarised below.

What are pharmaceutical payment policies?

Large quantities of healthcare funds are spent on medicines, and these amounts are increasing. Spending more on medicines could mean having less money for other healthcare or non-healthcare services. Also, misuse, overuse and underuse of appropriate medicines can lead to wasted resources and health hazards. Health insurers therefore are looking for ways of ensuring better use of medicines and controlling the costs of medicines, while still ensuring that patients get the medicines they need.

Patient payment policies vary with respect to the medicines included, the patient groups targeted, the amount of money patients are expected to pay and the ways in which they are expected to pay. Different policies may be used alone or together and include the following.

1. With a cap policy, patients are reimbursed for their prescription medicines up to a maximum amount, then are expected to pay costs higher than this amount.

2. With a fixed co-payment policy, patients pay a fixed amount per medicine or prescription.

3. With a co-insurance policy, patients pay a set percentage of the price of the prescription or medicine, rather than a fixed fee.

4. With a ceiling policy, patients pay full cost or part of the cost up to a certain amount, then are given medicines for free or at reduced cost.

These policies may lead people to use fewer medicines or to choose cheaper medicines. Although they may deter people from using unnecessary medicines, these policies may cause harm.

What happens when new payment policies are introduced?

Policies that increase the amount of money people have to pay for medicines may reduce insurers' medicine expenditures and may reduce patients' medicine use. They may result in a reduction in patients' use of life-sustaining medicines or other medicines that are important

for their health. These types of policies also may lead to small decreases in or uncertain effects on patients' use of healthcare facilities. No studies have looked at the effects of these policies on patients' health.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Caps

Patient or population: vulnerable and general populations

Settings: high-income countries (USA and Australia)

Intervention: more restrictive caps in terms of time of coverage or number of prescriptions

Comparison: no restrictions or less restrictive caps

Outcomes	Impact	Number of studies	Certainty of the evidence (GRADE)	Plain language summary	Comments
Medicine use					
Overall use of medicines	Moderate decrease	3 (2 ITS[1],1 RMS[2])	⊕⊕⊖⊖ Low	Intervention may decrease use of medicines for symptomatic conditions and overall use of medicines. Effect on use of medicines for asymptomatic conditions was not reported	Introduction of a cap policy reduced overall use of medicines and use of medicines for symptomatic conditions in vulnerable populations in Australia and in the USA. 1 study found an increase in the size of prescriptions and a larger reduction in the number of prescriptions per month for patients using more than 3 medicines per month
Use of medicines for symptomatic conditions	Moderate decrease	3 (1 ITS[3], 2 RMS[4])	⊕⊕⊖⊖ Low		
Use of medicines for asymptomatic conditions	No studies	0	–		
Cost					
Patient perspective	No studies	0	–	Intervention may decrease insurer expenditures on medicines. Effects on patient expenditures on medicines and on insurer expenditures on health care were not reported	Introduction of a cap policy reduced Medicaid expenditures for medicines for vulnerable populations in the USA. The extent to which insurer savings were passed on as increased patient expenditures is uncertain as no studies reported patient expenditures
Insurer perspective (expenditures on medicines)	Moderate decrease	3 (1 ITS[3], 2 RMS[4])	⊕⊕⊖⊖ Low		
Insurer perspective (expenditures on health care)	No studies	0	–		
Healthcare utilisation					
Overall healthcare utilisation	No studies	0	–	Effect of the intervention on emergency department use, hospitalisations or use of outpatient care is uncertain	Introduction of a cap policy increased emergency department use, hospitalisations and use of outpatient care in vul-

Emergency department and hospitalisation	Small increase	2 (1 ITS[3], 1 RMS[5])	⊕⊖⊖⊖ Very low[6]	nerable populations in the USA. However, the certainty of the evidence is very low
Outpatient care	Moderate increase	1 RMS[5]	⊕⊖⊖⊖ Very low[7]	
Health outcomes	No studies	0	–	No studies were found that reported effects of this intervention on health outcomes

GRADE Working Group grades of evidence.
High certainty: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different† is low.

Moderate certainty: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different† is moderate.
Low certainty: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different† is high.
Very low certainty: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different† is very high.

†

Substantially different = a large enough difference that it might affect a decision.

1. Soumerai 1991; Donnelly 2000.
2. Soumerai 1987.
3. Cromwell 1999.
4. Soumerai 1987; Soumerai 1994.
5. Soumerai 1994.
6. Downgraded because of imprecision issues.
7. Downgraded because of publication bias.

Summary of findings 2. Caps with co-insurance and ceiling

Patient or population: vulnerable population: senior 65 years of age or older

Settings: USA

Intervention: implementation of Medicare part D (cap combined with ceiling and co-insurance)

Comparison: heterogeneous but limited medicines coverage

Outcomes	Impact	Number of studies	Certainty of the evidence (GRADE)	Plain language summary	Comments

Medicine use					
Overall use of medicines	Small increase	1 RMS[1]	⊕⊕⊖⊖ Low	Intervention may increase overall use of medicines as well as use of medicines for symptomatic and asymptomatic conditions	Impact of the intervention varied according to previous medicines coverage. When prepolicy medicines coverage was more restrictive to patients, impact was higher. Intervention increased the use of symptomatic and asymptomatic medicines in vulnerable populations in the USA
Use of medicines for symptomatic conditions	Moderate increase	4 (2 ITS[2]; 2 RMS[3])	⊕⊕⊖⊖ Low		
Use of medicines for asymptomatic conditions	Small increase	2 (ITS[4]; RMS[5])	⊕⊕⊖⊖ Low		
Cost					
Patient perspective	Moderate decrease	5 (2 ITS[6]; 3 RMS[7])	⊕⊕⊖⊖ Low	Intervention may decrease patient expenditures on medicines. Effect on healthcare expenditures was not reported	Although the policy may lead to a moderate decrease in patient costs, 1 study showed an important increase in patient expenditures (+91%) on benzodiazepines. This occurred because this drug was excluded from the approved formulary for this policy
Insurer perspective (expenditures on medicines)	No studies	0	–		
Insurer perspective (expenditures on health care)	No studies	0	–		
Healthcare utilisation					
Overall healthcare utilisation	No studies	0	–	No studies were found that reported effects of this intervention on healthcare utilisation	-

Emergency department and hospitalisation	No studies	0	–	
Outpatient care	No studies	0	–	
Health outcomes	No studies	0	–	No studies were found that reported effects of this intervention on health outcomes –

GRADE Working Group grades of evidence.
High certainty: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different† is low.
Moderate certainty: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different† is moderate.
Low certainty: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different† is high.
Very low certainty: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different† is very high.

†

Substantially different = a large enough difference that it might affect a decision.

1. Yin 2008.
2. Chen 2008b; Shrank 2008.
3. Schneeweiss 2009; Polinski 2012.
4. Shrank 2008.
5. Schneeweiss 2009.
6. Shrank 2008; Polinski 2012.
7. Yin 2008; Schneeweiss 2009; Zhang 2009b.

Summary of findings 3. Fixed co-payment

Patient or population: seniors and general population

Settings: high-income countries (US, CN, Sweden)

Intervention: implementation of or increase in fixed co-payment

Comparison: lower value of fixed co-payment or full medicines coverage

Outcomes	Impact	Number of studies	Certainty of the evidence (GRADE)	Plain language summary	Comments
Medicine use					

Overall use of medicines	Small decrease	2 (ITS[1])	⊕⊖⊖⊖ Very low[5]	Effect of intervention on overall use of medicines is uncertain. However, it may decrease use of medicines for symptomatic and asymptomatic conditions	Use of all medicines in these studies decreased after implementation of/increase in co-payment, with the exception of oral hypoglycaemics, for which the increase in co-payment was low
Use of medicines for symptomatic conditions	Small decrease	3 (ITS[2])	⊕⊕⊖⊖ Low		
Use of medicines for asymptomatic conditions	Small decrease	3 (ITS[3])	⊕⊕⊖⊖ Low		
Cost					
Patient perspective	No studies	0	–	Intervention may slightly decrease insurer expenditures on medicines. Effect on patient expenditures and insurer expenditures on health care was not reported	Magnitude of decrease in insurer expenditures on medicine was variable, ranging from -16.9% to 0.1%
Insurer perspective (expenditures on medicines)	Small decrease	3 (ITS [4])	⊕⊕⊖⊖ Low		
Insurer perspective (expenditures on health care)	No studies	0	–		
Healthcare utilisation					
Overall healthcare utilisation	No studies	0	–	No studies were found that reported effects of this intervention on healthcare utilisation	-
Emergency department and hospitalisation	No studies	0	–		
Outpatient care	No studies	0	–		
Health outcome	No studies	0	–	No studies were found that reported effects of this intervention on health outcomes	-

GRADE Working Group grades of evidence.
High certainty: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different† is low.

Moderate certainty: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different† is moderate.
Low certainty: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different† is high.
Very low certainty: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different† is very high.

†

Substantially different = a large enough difference that it might affect a decision.

1. Nelson 1984; Hux 1997.

2. Hux 1997; Ong 2003; Reeder 1985
3. Reeder 1985; Hux 1997; Roblin 2005
4. Sawyer 1982; Nelson 1984; Hux 1997.
5. Downgraded because of risk of bias.

Summary of findings 4. Tier with fixed co-payment

Patient or population: vulnerable population (retirees and low income)

Settings: USA

Intervention: implementation of/increase in tier combined with fixed co-payment

Comparison: full medicine coverage/2-tier

Outcomes	Impact	Number of studies	Certainty of the evidence (GRADE)	Plain language summary	Comments
Medicine use					
Overall use of medicines	Uncertain	2 (ITS[1]; CBA[2])	⊕⊕⊖⊖ Low[3]	Intervention may lead to little or no difference in overall use of medicines and in use of medicines for symptomatic and asymptomatic conditions	These 2 studies had important differences in population characteristics and in the preintervention policy. Whereas the CBA study evaluated the shift from a 2-tier to a 3-tier plan for retired elderly, the ITS study evaluated implementation of cost sharing on people eligible for Medicaid (health insurance - including medicines - for low-income people in the USA). These 2 differences could explain the differences in results. Although the ITS study found a decrease in medicines use, this was not the case for the CBA study, which found mixed results across the different groups assessed. However, these studies found very small differences in the magnitude (increase or decrease) of medicines use
Use of medicines for symptomatic conditions	Uncertain	1 (CBA[1])	⊕⊕⊖⊖ Low		
Use of medicines for asymptomatic conditions	Uncertain	1 (CBA[1])	⊕⊕⊖⊖ Low		
Cost					

Patient perspective	No studies	0	–	No studies were found that reported effects of the intervention on costs	-
Insurer perspective (expenditures on medicines)	No studies	0	–		
Insurer perspective (expenditures on health care)	No studies	0	–		
Healthcare utilisation					
Overall healthcare utilisation	No studies	0	–	Effect of the intervention on use of emergency department, hospitalisation and outpatient care is uncertain. Effect on overall healthcare utilisation was not reported	It is important to highlight that the increase in co-payments for medicines was implemented alongside an increase in co-payment for health services. However, no differences between pre-policy and postpolicy periods were found during the study (2-year follow-up)
Emergency department and hospitalisation	Uncertain	1 (ITS[1])	⊕⊖⊖⊖ Very low[4]		
Outpatient care	Uncertain	1 (ITS[1])	⊕⊖⊖⊖ Very low[4]		
Health outcomes	No studies	0	–	No studies were found that reported effects of this intervention on health outcomes	

GRADE Working Group grades of evidence.
High certainty: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different† is low.

Moderate certainty: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different† is moderate.
Low certainty: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different† is high.
Very low certainty: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different† is very high.

†

Substantially different = a large enough difference that it might affect a decision.

1. Hartung 2008.
2. Huskamp 2007
3. Downgraded because of inconsistency.
4. Downgraded because of imprecision.

Summary of findings 5. Ceiling with fixed co-payment

Patient or population: low-income/general population

Settings: high-income countries (Australia, Canada and Sweden)

Intervention: implementation of or increase in ceiling combined with fixed co-payment

Comparison: full medicines coverage, lower fixed co-payment and ceiling amounts

Outcomes	Impact	Number of studies	Certainty of the evidence (GRADE)	Plain language summary	Comments
Medicine use					
Overall use of medicines	Small decrease	5 (4 ITS[1], 1 CBA[2])	⊕⊖⊖⊖ Low	Intervention may slightly decrease overall use of medicines and use of medicines for symptomatic and asymptomatic conditions	Effect varies according to pharmaceutical groups, ranging from no effect to a reduction of approximately 25%. Reduction in medicines use was higher for symptomatic medicines However, 1 study showed an increase in statin utilisation
Use of medicines for symptomatic conditions	Small decrease	6 (1 RMS[3]; 4 ITS[4]; 1 CBA[2])	⊕⊖⊖⊖ Low		
Use of medicines for asymptomatic conditions	Small decrease	4 (3 ITS[5]; 1 CBA[2])	⊕⊖⊖⊖ Low		
Cost					
Patient perspective	No studies	–	–	Effect of the intervention on insurer medicine expenditures is uncertain. Effect on patient medicine expenditures or insurer expenditure on health care was not reported	-
Insurer perspective (expenditures on medicines)	Small decrease	2 (ITS[6])	⊕⊖⊖⊖ Very low[8]		
Insurer perspective (expenditures on health care)	No studies	–	–		
Healthcare utilisation					
Overall healthcare utilisation	No studies	–	–	Intervention may lead to little or no difference in emergency department, hospitalisation and outpatient care	-
Emergency department and hospitalisation	No increase	1 (RMS[7])	⊕⊖⊖⊖ Low		

Outpatient care	No increase	1 (RMS[7])	⊕⊕⊖⊖ Low	
Health outcomes	No studies	–	–	No studies were found that reported effects of this intervention on health outcomes

GRADE Working Group grades of evidence.
High certainty: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different† is low.

Moderate certainty: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different† is moderate.
Low certainty: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different† is high.
Very low certainty: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different† is very high.

†

Substantially different = a large enough difference that it might affect a decision.

1. Andersson 2006; McManus 1996; Hynd 2008; Hynd 2009.
2. Poirier 1998.
3. Dormuth 2006.
4. McManus 1996; Hynd 2008; Wang 2008b; Hynd 2009.
5. Caetano 2006; Hynd 2008; Hynd 2009.
6. Andersson 2006; Dormuth 2009.
7. Dormuth 2008.
8. Downgraded due to risk of bias.

Summary of findings 6. Ceiling with co-insurance

Patient or population: general population

Settings: Canada, EUA and Sweden

Intervention: implementation of/increase in value of ceiling combined with co-insurance

Comparison: full medicines coverage, fixed co-payment and lower co-insurance

Outcomes	Impact	Number of studies	Certainty of the evidence (GRADE)	Plain language summary	Comments
Medicine use					
Overall use of medicines	Low decrease	3 (RCT[1], ITS[2], RMS[3])	⊕⊕⊕⊖ Moderate	Intervention probably slightly decreases overall use of medicines. It may also decrease use of medicines for	Differences in the direction of change were likely related to the prepolicy period. A greater reduc-

Use of medicines for symptomatic conditions	Medium decrease	5 (RCT[1]; 3 ITS[4]; RMS[5])	⊕⊖⊖⊖ Low	symptomatic conditions. Effects on use of medicines for asymptomatic conditions are uncertain	tion was noted in use of symptomatic medicines, with the exception of asthma inhalers, which experienced a slight increase in use (around 3%)
Use of medicines for asymptomatic conditions	Low decrease	2 ITS[6]	⊕⊖⊖⊖ Very low[8]		
Cost					
Patient perspective	No studies	–	–	Intervention probably slightly decreases insurer expenditures on medicines. Effects on patient expenditure or insurer expenditures on health care were not reported	Although all results showed a small decrease in costs from the insurer perspective, a small increase in insurer expenditures for medicines following the first year of the change from a fixed co-payment policy to a co-insurance policy
Insurer perspective (expenditures on medicines)	Low decrease	2 (RCT[1]; ITS[2])	⊕⊕⊕⊖ Moderate[9]		
Insurer perspective (expenditures on health care)	No studies	–	–		
Healthcare utilisation					
Overall healthcare utilisation	No studies	–	–	Intervention may lead to an increase in emergency department utilisation and hospitalisation. Effects of the intervention on outpatient care are uncertain. Effects on overall healthcare utilisation were not reported	This study assessed hospitalisation and physician visits related to chronic obstructive pulmonary disease, asthma or emphysema. A larger increase in hospitalisations than in physician visits was noted for these diseases following implementation of the policy
Emergency department and hospitalisation	Medium increase	1 RMS[7]	⊕⊕⊖⊖ Low		
Outpatient care	Low increase	1 RMS[7]	⊕⊖⊖⊖ Very low[10]		
Health outcomes	No studies	–	–	No studies were found that reported effects of this intervention on health outcomes	

GRADE Working Group grades of evidence.
High certainty: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different† is low.

Moderate certainty: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different† is moderate.
Low certainty: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different† is high.
Very low certainty: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different† is very high.

†

Substantially different = a large enough difference that it might affect a decision.

1. Newhouse 1993.
2. Andersson 2006.
3. Tamblyn 2001.
4. Blais 2002; Ong 2003; Wang 2008b.
5. Dormuth 2006.
6. Blais 2002; Caetano 2006.
7. Dormuth 2008.
8. Downgraded because of indirectness.
9. Downgraded because of risk of bias.
10. Downgraded because of imprecision.

BACKGROUND

The World Health Organization (WHO) considers equitable access to safe and affordable medicines as vital for achieving the highest possible standard of health for all. Nevertheless more than half of all medicines are prescribed, dispensed or sold inappropriately, and half of all patients do not take them correctly. This results in wastage of scarce resources and widespread health hazards, adverse reactions and drug resistance (WHO 2010).

Simultaneously, growing expenditures on prescription medications represent a major challenge to public policies and health spending by governments and other payers (Ess 2003; Freemantle 1996; Noyce 2000).

Various pharmaceutical policies are implemented by governments and other third-party payers to control expenditures and facilitate rational medicine use. This is the first update of the original review (Austvoll-Dahlgren 2008) performed as part of a series that focuses on the effects of such policies (Aaserud 2006a). In this review, we summarise what is known from well-designed research on the effects of policies regarding direct patient payments for medicines.

Many countries and jurisdictions have systems of pharmaceutical coverage, public or private (WHO 2010). These systems can be public or private, compulsory or voluntary. Pharmaceutical coverage is a way of economically securing people's access to important medicines, and is a way of spreading or diversifying the risk of heavy economic burdens for people who need affordable medicines. Thus public health and equity motives are often important for establishing pharmaceutical insurance systems.

One downside of pharmaceutical coverage is the danger of the so-called moral hazard (Rice 2004). Pharmaceutical insurance premiums (through taxes or premiums) are indirect patient payments for medicines. These payments are not related to specific medicines. After the pharmaceutical insurance premium has been paid, the price for products is theoretically zero for patients (unless other bureaucratic costs apply). This may give patients an economic incentive to use more medicines than they need. Thus, if a third party pays all the costs, patients can be expected to have higher utilisation rates for medicines (Gross 1994).

Description of the condition

Growing expenditures on prescription medicines represent a major challenge to many health systems. Cap and co-payment (direct cost-share) policies are intended as a disincentive to deter unnecessary or marginal utilisation, and to reduce third-party payer expenditures by shifting parts of the financial burden from insurers to patients, thus increasing their financial responsibility for prescription medicines.

By reducing the financial burden for third-party payers and facilitating rational use of medicines, saving resources and reallocating them to other healthcare services may lead to improved health (Gibson 2003; Reeder 1993). However, the effects of pharmaceutical policies are multi-dimensional (Ess 2003). The success of a pharmaceutical policy should be measured not only by its effect on the use and costs of medicines, but also by its effects on health, use of healthcare services and costs for patients, as well as for insurers. An overly restrictive pharmaceutical policy may have unintended consequences. For example, a shift of cost from insurer to consumer in low-income or other vulnerable populations may lead to discontinuation of necessary medicines, which may cause deterioration of health and increased healthcare utilisation and expenditures for patients and for insurers (Austvoll-Dahlgren 2008).

Description of the intervention

Categories of direct patient medication payment policies

Direct patient medication payment policies are diverse, relying on different mechanisms. They vary with respect to medicines included, patient groups targeted, intensity (size of co-payments), exemptions, enforcement and units on which payments are imposed (prescriptions, items, doses, expenditures). Various terms and definitions may be used to describe these policies. We have pragmatically categorised them into five main groups, based on policy intentions and mechanisms in a neutral regulatory environment. In real life, pharmaceutical policies are implemented separately, or they are combined with other pharmaceutical policies in complex settings involving other health polices and regulations.

Direct patient medication payment policies include caps (maximum numbers of prescriptions or medicines reimbursed), fixed co-payments (patients pay a fixed amount per prescription or medicine), co-insurance (patients pay a percentage of the price), ceilings (patients pay the full price or part of the cost up to a ceiling, after which medicines are free or are available at reduced cost) and tier co-payments (differential co-payments usually assigned to generic and brand medicines).

Caps

A cap is a prescription limit that allows unconstrained (zero-price) purchase by the patient of a certain number or volume of prescriptions, medicines or doses over a defined period of time; a cap imposes full patient payment of the market price after the limit has been reached. Caps may be applied to less cost-effective prescription medicines with the aim of reducing their use. Alternatively, they may be applied to all prescription medicines covered by the plan, with the aim of influencing patients and physicians to prioritise use of the most important medicines. Another intention is to reduce overall medicine use, while reducing plan expenditures by shifting some of the financial responsibility from the insurer to the patient. Multi-medicine users are particular vulnerable to this policy, as they are most likely to need prescriptions beyond the cap, especially when life-sustaining or other important medicines are included. As many multi-medicine users are elderly or have chronic conditions, this policy may have unintended effects on vulnerable populations. Patients whose medication use does not exceed the cap limit will have full pharmaceutical coverage.

Fixed co-payments

A fixed co-payment is a payment by the patient of a fixed amount per medicine or prescription. This is also called a prescription charge, a consumer charge, a prescription fee, a patient fee or cost sharing. The aim of a fixed co-payment is to reduce overall medicine expenditures and utilisation. As co-payments are the same for every prescription or for the whole medicine group, patients' co-payments are identical for both brand and generic medicines. Therefore fixed co-payments do not provide incentives

to choose cheaper substitutions, in contrast to co-insurance or tier co-payments.

Co-insurance

Co-insurance is a co-payment based on a set percentage of the price of a prescription or medicine, rather than a fixed fee. This is sometimes also called co-payment or cost sharing. Co-insurance provides an incentive for patients to choose cheaper medicines. Otherwise, co-insurance is similar to fixed co-payment, in that the policy aims to reduce overall medicine expenditures and utilisation.

Ceilings

A ceiling is a maximum contribution policy whereby patients must pay full cost or part of the cost (when combined with a fixed co-payment or co-insurance) up to a certain amount per defined period of time. After the ceiling has been reached by the patient, medicines are free or are available at reduced cost. This is sometimes called a maximum contribution, a deductible or a safety net. A maximum contribution policy is a more friendly policy towards patients with chronic conditions and multi-medicine users, who are most likely to exceed the ceiling. Other patients who receive only a few prescriptions during the period will not benefit. This policy may be hard on low-income populations, depending on how high the ceiling has been set. Ceiling policies may introduce a hoarding effect after the ceiling is reached.

Tier co-payments

Tier co-payment structures commonly assign generic medicines the lowest co-payment (first tier), and brand medicines (second tier) higher co-payments. If the structure is a three-tier system, the second tier is assigned to preferred brand medicines and the third tier to non-preferred brand medicines. Tier co-payments, which are also called incentive-based formularies or differential co-payments, encourage consumers through financial incentives to choose products that are assumed to be more cost-effective for the insurer. With this policy, one would expect reductions in total medicine use, compared with no co-payment, and a shift from expensive brand medicines towards cheaper second- or first-tier medicines. This shift is expected to further reduce expenditures for the insurer, but may increase expenditures for patients unwilling to substitute cheaper medicines, or when substitution is not possible. Tier structures may also give insurers greater bargaining power to negotiate rebates with pharmaceutical manufacturers. In this way, tier structures have similar features to formularies and reference pricing systems (Aaserud 2006).

Other cost-share policies not included in this review

The design, mechanisms and intended effects of different categories of pharmaceutical policies may overlap. For example, policies that set reimbursement prices, like reference pricing (Aaserud 2006), are similar to co-payment policies, in that both influence what the third-party payer and the patient will pay for medicines. The difference is that patients can choose to use the reference medicine and thus not have to pay a reference premium, whereas with co-payments, patients have to pay a portion of the cost regardless of which medicine they use within a medicine group.

Another related group of policies consists of formularies. These policies define a list of medicines that are reimbursed or recommended by the insurer. If the physician prescribes non-formulary medicines, or if the patient chooses to purchase medicines outside this list, the cost must be covered fully or in part by the patient. Formularies range from open informational lists to partially closed lists restricting selected medicines to closed formularies. Instead of including medicines on the list on the basis of criteria of efficacy, safety and cost-benefit measures (Dewa 2003; Jang 1988), tier structures use differentiated payments to facilitate substitution from brand to generic medicines. Although they are similar to tier co-payments in many ways, formularies do not offer patients the same financial responsibility. Nevertheless, the policies overlap and are often combined. For example, tier co-payments are often referred to as incentive-based formularies or multi-tier formularies. Likewise, formulary policies are often combined with different types of co-payments.

Reference pricing and formulary policies are addressed in separate reviews (Aaserud 2006a).

How the intervention might work

As they shift part of the financial burden from insurers to patients, thus increasing patient financial responsibility for prescription medicines (Gibson 2003; Reeder 1993), direct cost-share policies are intended as an incentive to deter overuse of medicines and use of medicines of limited efficacy and those used for conditions for which other, more cost-effective treatments are available, and to reduce third-party payer expenditures. Moreover, direct cost sharing may reduce the price of medicines through market mechanisms (Huttin 1994).

Patients are expected to respond to direct payments by:

1. decreasing medicine use, either overall or for medicines of limited value;
2. shifting to cheaper medicines; or
3. paying more out of pocket, thus shifting costs from insurers to patients.

Modifying factors

The impact of implementing direct patient payments for medicines varies with the intensity of the intervention, the type of payment (fixed co-payment, co-insurance, etc.), the length of the period the restriction encompasses (for caps and co-payment ceilings) and the units on which payments are imposed (i.e. prescriptions, items, doses or expenditures). How patients react to these policies depends on price elasticity.

The price elasticity for a medicine is the percentage change in its consumption related to one percentage change in the price or charge that patients pay for that medicine (Domino 2003; Huttin 1994; Johnston 1991). This is a measure of how sensitive pharmaceutical consumption is to changes in pharmaceutical prices, and indirectly to changes in co-payments. High-income patients and patients in greater need of medicines are expected to be less sensitive to co-payments (Smith 1992). The effect on patients' pharmaceutical use may be unchanged if they value the medicine as more important than the burden of cost sharing and choose to pay the increased pharmaceutical expenditures to sustain their medicine use. However, several other factors may modify the impact of direct payment policies (see Table 1), including:

1. size of cap/co-payment;
2. drug groups included in the policy;
3. vulnerable populations;
4. enforcement;
5. information provided to patients and providers; and
6. exemptions.

Direct payment by patients for medicines is controversial because increased cost sharing for medicines may present a financial barrier to poor households or to patients with chronic conditions who need a larger volume of pharmaceuticals (Reutzel 1993; Soumerai 1990; Thomson 2004). Low-income populations may be particularly vulnerable to co-payments because they are more likely to be sick (Adams 2001). Other vulnerable groups can include pregnant women, children and the elderly (Rice 2004; Soumerai 1987).

Exemptions are often made to protect the disadvantaged (Ess 2003; Haaijer-Ruskamp 2002; Mossialos 2004). However, exemptions reduce potential savings for the insurer. Exemptions can be embedded in the policy for certain medicines or patient groups on the basis of specific criteria, such as disease, age or income (Gross 1994). One mechanism for providing exemptions is prior authorisation, whereby reimbursement for a restricted prescription may be permitted for patients who fulfil set criteria (Martin 1996a). Another loophole for co-payment per prescription policies involves allowing prescribers to increase the volume (doses) allowable per prescription or prescription item (Soumerai 1987).

Enforcement of the policy of exemption may have an impact on the effect of the policy. Physicians or pharmacists may decide to exempt patients from the policy; however, they may then be accountable for the co-payment instead of the patient.

How involved patients are in decision making and how much information is provided to prescribers or pharmacists are important factors. If physicians rather than patients determine which medicines are prescribed, they might not be as sensitive to higher patient payments. The extent to which they are informed about the price of medicines, medicine substitution possibilities and the patient's ability to pay can affect the impact of direct payment policies. If prescribers are not well informed, the use of medicines may not change, and the economic burden on patients may increase.

The information provided to patients is important because their decisions may depend on their knowledge about their health and about the effects of different medicines. Critics argue that because most patients lack relevant knowledge, they may be at risk of relinquishing medicines with important health effects instead of medicines that are less essential (Levy 1992; Lexchin 2002).

Why it is important to do this review

Pharmaceutical policies are being changed or implemented in many countries. Price and affordability are important determinants of access to medicines. Therefore, decisions about direct patient payments for medicines should be informed by evidence about the effects of those policies on use of medicines, costs, utilisation of health services and health outcomes.

Our aim in this review is to support informed decisions about cap and co-payment policies while guiding future evaluations by updating (from 2008 to 2013) a summary of what is known from well-designed research about the effects of these policies on rational (appropriate and efficient) use of medicines.

OBJECTIVES

To determine the effects of cap and co-payment policies on rational use of medicines, healthcare utilisation, health outcomes and costs (expenditures).

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs), non-randomised controlled trials (NRCTs), repeated measures (RM) studies, interrupted time series (ITS) studies and controlled before-after (CBA) studies.

We used the Effective Practice and Organisation of Care Group (EPOC) definition of RCT, NRCT, CBA, ITS and RM studies. Interrupted time series (ITS) and RM studies use observations at multiple time points before and after an intervention (the 'interruption'), along with a clearly defined point in time when the intervention occurred and at least three data points before and three after the intervention (EPOC 2013a). We excluded studies that did not have a clearly defined point in time when the intervention occurred and at least three data points before and three after the intervention. RCTs, NRCTs and CBA studies had to have at least two control and two intervention sites. In studies with only one intervention or control site, the intervention (or comparison) was completely confounded by study site, making it difficult to attribute observed differences to the intervention rather than to other site-specific variables. We included both single-arm and controlled ITS and RM studies. However, controlled ITS and RM studies are similar to CBA studies; the same exclusion criterion used for other controlled studies was used to decide whether the comparison in controlled ITS and RM studies should be included, and the exclusion criteria for ITS and RM studies were used to decide whether the uncontrolled (intervention site) analyses should be excluded from those studies.

Because of this change to the selection criteria (excluding controlled studies with only one intervention or control site), we reviewed all previously included controlled studies and excluded those with only one intervention or control site. All studies excluded for this reason are listed in the Characteristics of excluded studies table.

Types of participants

Healthcare consumers and providers within a large jurisdiction or system of care. Jurisdictions could be regional, national or international. We included studies conducted within organisations, such as health maintenance organisations, if the organisation was multi-sited and served a large population.

Types of interventions

Policies that regulate patients' out-of-pocket payments for medicines, including increases and decreases in the amount paid directly by patients, limits on the amount paid by patients and limits on the amount reimbursed, including caps, fixed co-payments, co-insurance, maximum co-payment ceilings and tier

co-payments. We defined policies in this review as laws, rules or financial or administrative orders made by governments, non-government organisations or private insurers. We did not include interventions provided at the level of a single facility. However, we did include pilot studies of a proposed policy evaluated at a single facility serving a large population.

Types of outcome measures

Primary outcomes

To be included, a study had to have an objective measure of at least one of the following outcomes.

1. Medicine use.
2. Healthcare utilisation.
3. Health outcomes.
4. Costs (expenditures), including medicine expenditures and prices and other healthcare and policy administration expenditures.

Secondary outcomes

None.

Search methods for identification of studies

We applied no language restrictions in this search.

Electronic searches

We provided the search strategies used for the previous version of this review in Appendix 1. Databases searched for this update are listed below.

1. Cochrane Central Register of Controlled Trials (CENTRAL), (including the Cochrane Effective Practice and Organisation of Care (EPOC) Group Specialised Register), Cochrane Library, searched on 27 January 2013 (Appendix 2).
2. MEDLINE Ovid (In-Process & Other Non-Indexed Citations), searched on 27 January 2013 (Appendix 3).
3. MEDLINE Ovid, 1946 to January Week 3 2013, searched on 27 January 2013(Appendix 4).
4. EMBASE Ovid, 1980 to Week 4 2013, searched on 27 January 2013 (Appendix 5).
5. IPSA (International Political Science Abstracts) EBSCO, searched on 27 January 2013 (Appendix 6).
6. EconLit ProQuest, 1969 to present, searched on 27 January 2013 (Appendix 7).
7. Worldwide Political Science Abstracts ProQuest, 1975 to present, searched on 27 January 2013 (Appendix 7).
8. PAIS International, Public Affairs Information Service ProQuest, 1914 to present, searched on 27 January 2013 (Appendix 7).
9. International Network for Rational Use of Drugs (INRUD) Bibliography, searched on 28 January 2013 (Appendix 8).
10. World Health Organization Library Information System (WHOLIS), the WHO library database, searched on 28 January 2013 (Appendix 9).
11. Latin American and Caribbean Health Sciences Literature (LILACS), searched on 28 January 2013 (Appendix 10).
12. WHO Libraries African Index Medicus (AIM) (Regional Office for Africa (AFRO)), Index Medicus for the Eastern Mediterranean Region (IMEMR) (Regional Office for the Eastern Mediterranean (EMRO)), Index Medicus for the South-East Asia Region (IMSEAR) (Regional Office for the South-East Asia Region (SEARO)) and Western Pacific Region Index Medicus (WPRIM) (Regional Office for the Western Pacific Region (WPRO)) and Global Health Library WHO, searched on 28 January 2013 (Appendix 11).
13. PubMed searched on 31 January 2013 for relevant journals not indexed in MEDLINE (Appendix 12).
14. SCOPUS searched on 31 January 2013 (Appendix 13).
15. Scientific Electronic Library Online (SciELO) (BIREME), searched on 13 December 2011 (Appendix 14).

We used a modified version of the EPOC search strategy methodology filter to limit the MEDLINE strategy to randomised trials, controlled trials, time series analyses and controlled before-after studies.

Searching other resources

Trial registries

International Clinical Trials Registry Platform (ICTRP), World Health Organization (WHO) (http://www.who.int/ictrp/en/), searched on 23 March 2014 (Appendix 15).ClinicalTrials.gov, US National Institutes of Health (NIH) (http://clinicaltrials.gov/), searched on 23 March 2014 (Appendix 16).

Grey literature

1. OpenGrey (http://www.opengrey.eu/) searched on 25 February 2013 (Appendix 17).
2. Journal of Librarianship and Information Science (JOLIS), the Library Network serving the World Bank Group and the International Monetary fund (IMF), searched on 2 February 2013 (Appendix 18).
3. Organisation for Economic Co-operation and Development (OECD) Library, searched on 25 February 2013 (Appendix 19).
4. World Bank e-Library, searched on 25 February 2013 (Appendix 20).
5. World Health Organization (WHO), searched on 25 February 2013 (Appendix 21).
6. World Bank Documents & Reports, searched on 28 February 2013 (Appendix 22)

Data collection and analysis

Selection of studies

Two review authors (of VL, LA, RM, IE, EL, SA and GC) independently reviewed all search results, abstracts and reference lists of relevant reports. We retrieved the full text of potentially relevant reports (if one or both review authors thought it was potentially relevant), and two (of the above) review authors independently assessed the relevance of those studies and the risk of bias for included studies.

Data extraction and management

The lead author (VL) extracted data from included studies in collaboration with one other review author (LA, RM, IE, EL, SA and GC). For all steps in the above process, review authors resolved disagreements by discussion, when necessary including another review author.

We extracted the following additional information from included studies, using a standardised data extraction form.

1. Study type (randomised trial, non-randomised trial, repeated measures study, interrupted time series, controlled before-after).
2. Study setting (country, key features of the healthcare system, concurrent pharmaceutical policies).
3. Study sponsors.
4. Characteristics of participants (consumers, physicians, practices, hospitals, etc.).
5. Characteristics of the policies.
6. Main outcome measures and study duration.
7. Results for the main outcome measures.

The data extraction form included field codes, and once all data had been extracted, the information was imported into a spreadsheet, from which secondary spreadsheets were created to support performance of the analysis, reporting of results and preparation of 'Summary of findings' tables.

We included all outcomes that met the inclusion criteria. However, if the study presented results on the same outcome several times (e.g. by using different units) or across a large number of drug groups, we chose what we considered the most important outcomes for each of the four types of outcomes (medicine use, health, healthcare utilisation and expenditures), as specified by the study authors or based on discussions among the review authors. We included additional outcomes in accordance with the judgement of two review authors if the additional outcomes provided better insight into how a policy worked or did not work as expected, or if the additional outcomes provided an explanation for mechanisms or modifiers of the intervention. We did not base decisions about which outcomes to include on the direction or size of effect, or on whether a finding was statistically significant.

Assessment of risk of bias in included studies

We used the standard criteria recommended by EPOC to assess risk of bias for studies included in EPOC reviews (EPOC 2013b).

We used these criteria for assessing risk of bias for controlled studies.

1. Random sequence generation.
2. Allocation concealment.
3. Baseline outcomes similarity.
4. Baseline characteristics similarity.
5. Incomplete outcome data assessment.
6. Blinding of outcome assessment.
7. Protection against contamination.
8. Selective outcome reporting.
9. Other risk of bias.

We used these criteria for assessing risk of bias for ITS and RM studies.

1. Intervention independent of other changes (protection against secular changes).
2. Shape of the intervention prespecified.
3. Intervention unlikely to affect data collection (protection against detection bias).
4. Blinding of outcome assessment.
5. Incomplete outcome data assessment.
6. Avoidance of selective outcome reporting.
7. Other risk of bias.

For controlled ITS (CITS) and controlled RM (CRM) studies, we assessed the time series portion of the studies independently from the controlled comparison, using the criteria described above for ITS and RM studies. We assessed the control series portion of the study using the criteria for controlled studies provided above. If the control portion was found to have high risk of bias, we did not include it and classified the study as ITS or RM; otherwise we used the control data as a control in the review.

We graded our confidence in available estimates of effects using the approach recommended by the GRADE (Grades of Recommendation, Assessment, Development and Evaluation) Working Group (EPOC 2013b; Guyatt 2008).

Measures of treatment effect

The preferred analysis method for ITS and RM studies was regression analysis with time trends before and after the intervention, which adjusted for autocorrelation and periodic changes, or autoregressive integrated moving average (ARIMA) analysis or other techniques that adjusted for autocorrelation and secular trends. We presented the results for the outcomes as changes along two dimensions: change in level and change in slope.

Change in level, which is the immediate effect of the policy, is measured as the fitted value for the first postintervention data point (one month after the intervention) minus the predicted outcome one month after the intervention, based on the preintervention slope only.

Change in slope, which is the change in the trend from preintervention to post intervention, reflects the long-term effect of the intervention. As interpretation of the change in slope could be difficult, we chose to present the long-term effects similarly to how we calculated and presented the immediate effects. We presented the effects after half a year as the fitted value for the six-month postintervention data point (half a year after the intervention) minus the predicted outcome six months after the intervention, based on the preintervention slope only. We reported the effects after one year and after two years in the same way when they had been measured. For pharmaceutical expenditures, we also calculated the savings after a half-year, one year and two years as the area between predicted and actual expenditure curves.

Given that policy changes are often announced some months before official implementation, we defined a transition phase as six months from the official announcement of the policy. If included ITS and RM studies stated a different transition phase, we used the definition used by the studies. All results excluded transition phase data.

For studies that reported only the absolute change, we estimated the relative change in level from the expected level one observation post intervention. We calculated the expected level as the intercept value plus the prepolicy trend times the number of observations up to the first postintervention point. Then, we compared the expected prepolicy curve versus the observed one, and we calculated the relative change.

For CBA studies, we reported adjusted relative effects. For dichotomous outcomes, we reported, if possible, the risk ratio, adjusted for baseline differences in the outcome measure (i.e. risk ratio post intervention/risk ratio preintervention). For continuous variables, we reported, if possible, the relative change, adjusted for baseline differences in outcome measures (i.e. (the absolute postintervention difference between intervention and control groups - the absolute preintervention difference between intervention and control groups)/the postintervention level in the control group.

Unit of analysis issues

For controlled studies with a unit of analysis error, we attempted to obtain the intracluster correlation coefficient to perform an adjusted analysis. We adjusted results for clustering by multiplying the standard errors of the estimates by the square root of the design effect when the design effect was calculated as DEff = 1 + (M - 1) ICC, where M is the mean cluster size and ICC is the intracluster correlation coefficient. If an adjusted analysis was not possible, we did not report P values or confidence intervals for the estimate of effect.

Dealing with missing data

We tried to obtain missing data from study authors. When missing data could not be retrieved, we made no assumptions about the missing data (e.g. imputing data based on specific data) but reported only available data.

Assessment of heterogeneity

We made a qualitative assessment of the extent to which studies assessing a particular comparison were similar to one another, which included assessment of settings, interventions, participants and outcomes.

We had planned to obtain an initial visual overview of statistical heterogeneity by scrutinising the forest plots, while looking at the overlap between confidence intervals (CIs) around the estimate for each included study. We had also planned to quantify inconsistency across studies, and thus the impact of heterogeneity on the meta-analysis, using the I^2 statistic, and we had defined I^2 > 50% as indicative of substantial heterogeneity. However, these assessments were not possible, as no pooled analyses were undertaken.

Assessment of reporting biases

As a result of substantial variation in populations, contexts, interventions, comparisons and outcome measures, it was not possible to assess completely risk of publication bias (selective reporting of complete studies) on the basis of asymmetry in results of included studies. We tried to minimise this problem by searching for studies in a broad range of databases, while trying to cover both scientific and grey literature, in different regions and settings. We assessed selective outcome reporting together with other risks of bias for each included study (EPOC 2013b; Higgins 2011).

Data synthesis

If papers with an ITS design did not provide an appropriate analysis or report of the results (Cromwell 1999; Martin 1996a) but presented data points in a scannable graph or in a table, the data were reanalysed using the methods described in Ramsay 2003. The following segmented time series regression model was specified: Y(t) = B0 + B1*Pre-slope + B2*Post-slope + B3*intervention + e(t), where Y(t) is the outcome in month t. Pre-slope is a continuous variable indicating time from the start of the study up to the last point in the preintervention phase and coded constant thereafter. Post-slope was coded as 0 up to and including the first point post intervention and coded sequentially from 1 thereafter. The intervention was coded as 0 for preintervention time points, and as 1 for postintervention time points. In this model, B1 estimates the slope of the preintervention data, B2 estimates the slope of the postintervention data and B3 estimates the change in level of outcome as the difference between the estimated first point post intervention and the extrapolated first point post intervention, if the preintervention line was continued into the postintervention phase. The difference in slope is calculated by B2 - B1. The error term e(t) was assumed to be first-order autoregressive. We calculated confidence intervals (95%) for all effect measures.

In a repeated measures design, the data are repeated outcome measures from many individual patients. For studies with this design, we used results reported in the original papers, as any reanalysis would underestimate or overestimate the standard error of the effect sizes because it was not possible to adjust for correlation occurring within individuals.

For repeated measures and ITS studies with adequate analysis but with no appropriate effect sizes reported (Blais 2002; Tamblyn 2001), we reanalysed graphical displays of confidence intervals for projected postintervention estimates (based on preintervention data only), when these were available. The width of the newly derived effect size confidence interval was assumed to be the same as the width of the projected confidence interval in the original study analysis. Although imperfect, this approach should only marginally underestimate or overestimate the standard error of effect sizes. Given the pragmatic nature of this approach, we have highlighted reanalysed results when reanalyses were undertaken.

Reanalyses were performed, including calculation of percentage relative changes and, if needed, reanalysis of ITS data, using methods described in the EPOC resources for review authors (EPOC 2013c).

We prepared tables for each subcategory of intervention, which included the following information: study identification; characteristics of the intervention; drug use; healthcare utilisation; health outcomes and expenditures. We listed and described important policy options for which no evaluations were found. We graded our confidence in available estimates of effects (certainty of the evidence) (Table 2; Table 3; Table 4; Table 5; Table 6; Table 7), and we prepared 'Summary of findings' tables using the approach recommended by the GRADE Working Group (EPOC 2013d; Guyatt 2008).

We elected to present in 'Summary of findings' tables the following main outcomes.

1. Medicine use.
   a. Overall.
   b. Symptomatic.
   c. Asymptomatic.

2. Healthcare utilisation.
   a. Overall healthcare utilisation.
   b. Hospitalisations and emergency department visits.
   c. Outpatient care.
3. Cost.
   a. Insurer perspective (expenditures on medicines).
   b. Insurer perspective (expenditures on health care).
   c. Patient perspective (expenditures on medicines).
4. Health outcomes.

The decision to include in this update medicine use for symptomatic and asymptomatic conditions was based on research suggesting that patients' perceptions of the value of medicines depend on their perceptions of the condition being treated (Hynd 2008; Landsman2005; O'Grady 1985). This means that medicines for diseases with no, mild or few symptoms, such as hypertension, would be more likely to be discontinued when patients' out-of-pocket costs increase, even for essential medicines. On the other hand, medicines for conditions such as asthma, with frequent or severe symptoms, would be less likely to be discontinued. On the basis of this hypothesis, we divided all medicines into two categories: medicines for symptomatic conditions and medicines for asymptomatic conditions (Table 8). When data presented in the paper allowed, we reanalysed medicines in these groups of medicines. The set of medicines including both symptomatic and asymptomatic medicines was considered "overall". Additionally, some authors classified the index medicines as essential and non-/less essential; consequently, the results in these studies were reported according to this classification. In this last case, the authors' classification was respected.

At least two review authors prepared each 'Summary of findings' table. We elected to present the effects qualitatively rather than quantitatively in the 'Summary of findings' tables, as the quantitative results are described in the Results section, are difficult to summarise concisely quantitatively and may be difficult to understand.

We categorised the impact on each outcome according to the direction of the effect (increase, decrease, uncertain change or no meaningful change) and the magnitude of the change (small, moderate, large or very large). When studies indicated different directions of effect, we categorised the impact as uncertain. We also considered potential modifying factors (Table 1) and the certainty of the evidence when categorising the impact. We considered the magnitude of the change as “small” when it was less than 25%, “moderate” when it was 25% to 49%, “large” when it was 50% to 74% and “very large” when it was greater than 74%. We accomplished this division through group consensus. When results of a study were not expressed in relative percentage change, we discussed these results among the review authors and based this classification on a consensus decision reached by the review authors. Views on boundaries between these change categories may differ among stakeholders across settings, types of outcomes and anticipated effects. However, we believe these categories can help with interpretation of the evidence profiles.

Besides the “Outcome” and “Impact” columns, the 'Summary of findings' table reports “Number of studies”, “Certainty of the evidence” and "Comments". We used the "Comments" column to provide more in-depth explanations of the findings. We explore these points in greater detail in the Discussion section.

In addition, we attempted to identify important factors that might be considered by anyone contemplating implementation of any of the policy alternatives, including possible trade-offs (of expected benefits vs harms and costs); short-term versus long-term effects; indications and contraindications for when the policies might be used; limitations of available evidence; and other important factors that might affect translation of available evidence into practice in specific settings.

We present in Table 9 abbreviations used in this text.

Subgroup analysis and investigation of heterogeneity

We considered potential explanatory factors for heterogeneity as listed in Table 1, including differences in characteristics of the policies; differences in settings; and differences in study limitations. However, we did not identify sufficiently similar comparisons with similar outcomes to allow meaningful exploration of heterogeneity.

Sensitivity analysis

We performed no sensitivity analyses.

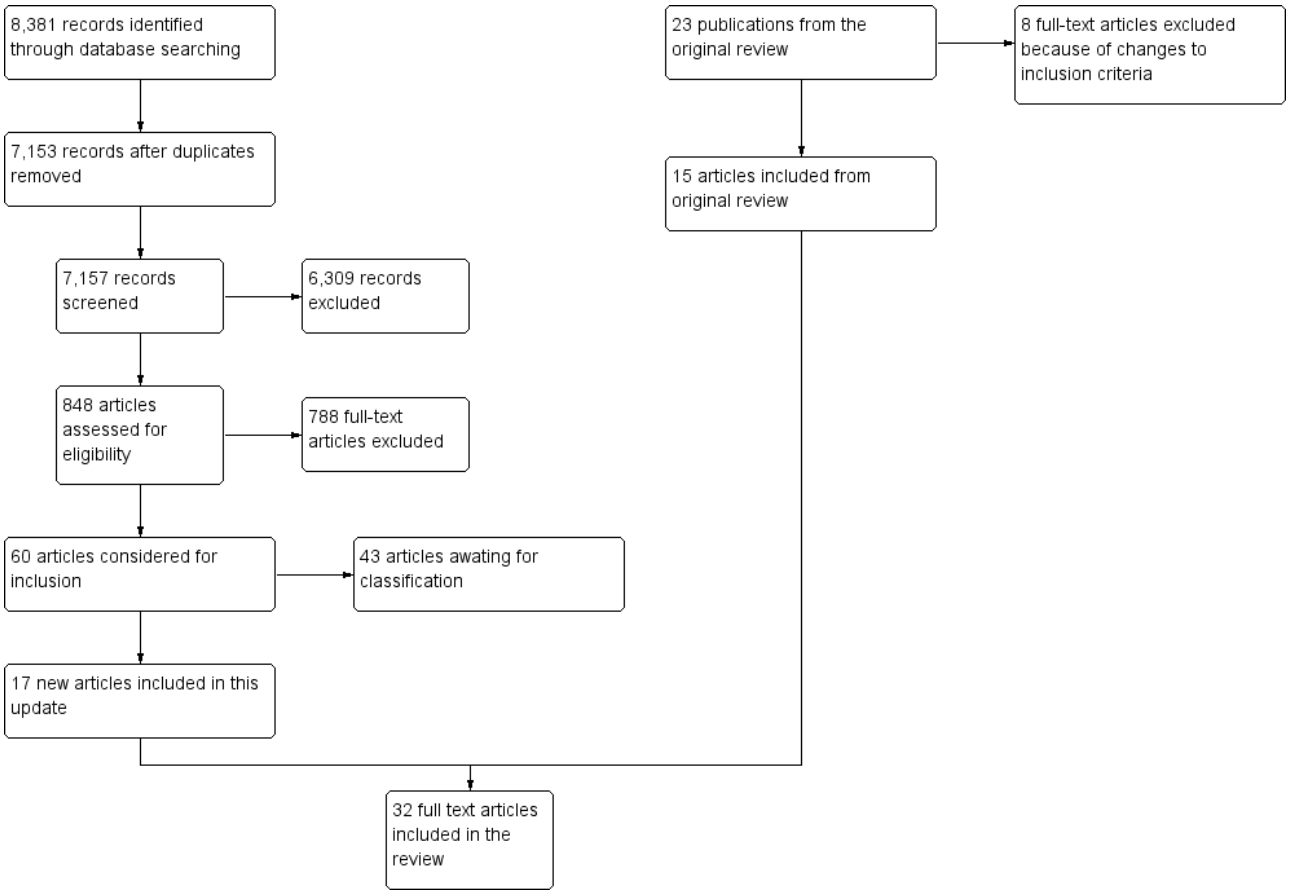
RESULTS

Description of studies

Results of the search

See the study flow diagram for this update (Figure 1). We screened approximately 22,000 references for the previous version of this review (Austvoll-Dahlgren 2008). Updated searches yielded 8381 new references published between 2008 and 2012. We retrieved full-text copies of 848 papers that were potentially relevant. We excluded 788 of these, in most cases because they did not meet the study design inclusion criteria. These were primarily reviews, editorials, modelling studies, cross-sectional studies and before-after studies without a control group.

Figure 1. Study flow diagram for this update.



We considered 60 full text articles for inclusion. We identified 43 studies that possibly met the inclusion criteria but were not assessed before completion of this update (see Characteristics of studies awaiting classification). We have not evaluated these studies because we were not able to retrieve full-text papers, and the abstracts did not provide sufficient information. Some of these were abstracts of presentations at conferences for which full papers have not yet been published.

Included studies

We included in this update 17 new papers reporting evaluations of 15 interventions. Some of the included studies reported on more than one intervention. Overall, 32 papers (Newhouse 1993 comprises five papers) reporting evaluations of 34 interventions met the inclusion criteria. In keeping with the exclusion criteria for controlled studies that were not used in the previous version of the review, we excluded from this update eight papers reporting evaluations of nine interventions that were included in the previous version of this review (Brian1974; Fryatt 1994a; Harris1990; Kozyrskyj2001; Lingle1987; Martin 1996a; Motheral1999; Motheral2001).

It is important to highlight that reanalysed results from one specific study (Dormuth 2006) differ from results published by the study author for two reasons.

1. Definition of outcomes reported: In the paper, results are reported as mean monthly use over a period of time (January 2002 to April 2003 for co-payment, May 2003 to June 2004 for income-based deductibles). If seasonality exists, effects of an intervention based on these means might be biased if the periods of time included in the mean do not match. In the reanalysis, the difference was estimated between predicted value from the autoregressive model with the intervention and predicted value from the autoregressive model with the assumption that the intervention had not been implemented at a given point in time (e.g. 12 months after implementation of an intervention).
2. Model used as the basis for results: The paper suggests that the model used includes only one interruption. If two interruptions had been included, a shift in the trend line should be observed after implementation of income-based deductibles. As the trend line shows an increase over time, the difference between predicted values based on preintervention trends and observed values will be larger for the income-based deductible intervention than for the co-payment intervention, even if the actual means of monthly use are the same for the two periods. All of the authors' conclusions are based on differences from predicted values based on preintervention trends.

Study designs

We included one RCT (Newhouse 1993); eight RM studies (Dormuth 2006; Dormuth 2008; Schneeweiss 2009; Soumerai 1987; Soumerai 1994; Tamblyn 2001; Yin 2008; Zhang 2009b); 21 ITS studies (Andersson 2006; Blais 2002; Caetano 2006; Chen 2008b; Cromwell 1999; Donnelly 2000; Dormuth 2009; Hartung 2008; Hux 1997;

Hynd 2008; Hynd 2009; McManus 1996; Nelson 1984; Ong 2003; Polinski 2012; Reeder 1985; Roblin 2005; Sawyer 1982; Shrank 2008; Soumerai 1991; Wang 2008b) and two CBA studies (Huskamp 2007; Poirier 1998).

For more information, please see the Characteristics of included studies table.

Characteristics of settings and interventions of included studies

Overall, eight interventions were evaluated in 17 publications in the USA (Chen 2008b; Cromwell 1999; Hartung 2008; Huskamp 2007; Nelson 1984; Newhouse 1993; Polinski 2012; Reeder 1985; Roblin 2005; Sawyer 1982; Schneeweiss 2009; Shrank 2008; Soumerai 1987; Soumerai 1991; Soumerai 1994; Yin 2008; Zhang 2009b), six interventions were evaluated in nine publications in Canada (Blais 2002; Caetano 2006; Dormuth 2006; Dormuth 2008; Dormuth 2009; Hux 1997; Poirier 1998; Tamblyn 2001; Wang 2008b), three interventions were evaluated in four studies in Australia (Donnelly 2000; Hynd 2008; Hynd 2009; McManus 1996) and five interventions were evaluated in two studies in Sweden (Andersson 2006; Ong 2003).

Three interventions (in five publications) were cap policies (Cromwell 1999; Donnelly 2000; Soumerai 1987; Soumerai 1991; Soumerai 1994), one intervention (in six publications) was a cap with co-insurance and a ceiling policy (Chen 2008b; Polinski 2012; Schneeweiss 2009; Shrank 2008; Yin 2008; Zhang 2009b), five interventions (in six publications) were fixed co-payment policies (Hux 1997; Nelson 1984; Ong 2003; Reeder 1985; Roblin 2005; Sawyer 1982), two interventions (in two publications) were tier co-payment with fixed co-payment policies (Hartung 2008; Huskamp 2007), six interventions (in 10 publications) were fixed co-payment with a ceiling policies (Andersson 2006; Caetano 2006; Dormuth 2006; Dormuth 2008; Dormuth 2009; Hynd 2008; Hynd 2009; McManus 1996; Poirier 1998; Wang 2008b) and nine interventions (in 10 publications) were co-insurance with a ceiling policies (Andersson 2006; Blais 2002; Caetano 2006; Dormuth 2006; Dormuth 2008; Dormuth 2009; Newhouse 1993; Ong 2003; Tamblyn 2001; Wang 2008b). See Table 10, Table 11, Table 12, Table 13, Table 14, Table 15 and Table 16 for further details.

The papers provided data on medicine use (19 studies), costs (17 studies) and healthcare utilisation (six studies). Data on costs were reported as medicine expenditures from the insurer's perspective (nine studies), medicine expenditures from the patient's perspective (six studies), healthcare expenditures (one study) and intervention costs (one study). None of the included studies reported health outcomes.

Excluded studies

The Characteristics of excluded studies table provides reasons for excluding studies. We included studies in this list if the exclusions are ones that we thought readers might question; if the studies are well known in the field but did not meet all of the inclusion criteria for this review; and if they are ITS studies that met all of the inclusion criteria except that they had an insufficient number of data points. We also listed the CBA studies included in the first version of this review that were excluded for this update because they have only one control or intervention site.

Risk of bias in included studies

For details on our assessments of risk of bias, see the 'Risk of bias' tables for each study (Characteristics of included studies). Overall we assessed low risk of bias for most of the criteria across those studies to which each criterion applied. However, we assessed high risk of bias for six of the 27 included ITS and RM publications because of the risk that the intervention was not independent of other changes (Andersson 2006; Dormuth 2006; Dormuth 2008; Dormuth 2009; Sawyer 1982; Wang 2008b). The two CBA studies had high risk of bias because of the risk of baseline differences (Huskamp 2007; Poirier 1998). Four publications had high risk of bias because outcome data were incomplete (Andersson 2006; Hux 1997; McManus 1996; Soumerai 1991).

Effects of interventions

See: **Summary of findings for the main comparison** Caps; **Summary of findings 2** Caps with co-insurance and ceiling; **Summary of findings 3** Fixed co-payment; **Summary of findings 4** Tier with fixed co-payment; **Summary of findings 5** Ceiling with fixed co-payment; **Summary of findings 6** Ceiling with co-insurance

1. Caps

Four cap policies were evaluated in three ITS (Cromwell 1999; Donnelly 2000; Soumerai 1991) and two RM study publications (Soumerai 1987; Soumerai 1994). A summary of the findings for cap policies is provided in Summary of findings for the main comparison, and additional details on each study are presented in Table 10.

Reimbursement restricted to three prescriptions versus no restrictions

Setting: 1981, low-income patients (Medicaid) in New Hampshire, USA (Soumerai 1987; Soumerai 1991; Soumerai 1994).

Risk of bias: RM/ITS studies with no serious limitations.

The introduction of this policy caused an immediate and sustained drop in medicine use. Soumerai 1987 analysed the effects of the intervention in two groups of patients: multi-medicine users, defined as those who had received an average of three or more prescriptions per month; and all other patients. Monthly medicine use per person in the cohort of multi-medicine users was reduced by 46.0% (P value < 0.05), and medicine use by other patients was reduced by 17.0% (P value < 0.05). A loophole was embedded into this cap policy, allowing physicians to triple the allowable quantity of pills, and during the cap period the average prescription size was increased by 13.0% (P value < 0.05) in the cohort of multi-medicine users (Soumerai 1987).

The same publication classified the medicines into three groups: "essential" (insulin, propranolol, thiazides, furosemide, methyldopa, lithium, digoxin, anxiolytic and hypnotic agents, depressants and lithium, antipsychotics); "symptomatic relief" (analgesics and anti-inflammatories); and "limited efficacy" drugs (ergoloid mesylates, barbiturate-anticholinergic combination agent Donnatal, propoxyphene without aspirin or acetaminophen, anticholinergic dicyclomine). Overall, a reduction of 58.0% (P value < 0.05) in monthly medicine use (per 100 eligible patients) was found for "limited efficacy" medicines. However, a reduction in "symptom-relieving" medicines (38.0%; P value < 0.05)

and in "essential" medicines (28.0%; P value < 0.05) was also noted (Soumerai 1987).

Reductions in medicine use were found in vulnerable subgroups of elderly patients (35.0%; P value < 0.001) (Soumerai 1991), and reductions in use of the following drugs were reported in severely disabled patients diagnosed with schizophrenia: antipsychotic agents (15.4%; P value < 0.003), anxiolytic and hypnotic agents (37.3%; P value < 0.001) and antidepressants and lithium (49.1%; P value < 0.001) (Soumerai 1994).

Overall, average reimbursements by the health insurer dropped by 38.0% (P value < 0.05) and medicine expenditures by the health insurer were decreased by 19.0% per patient per month (P value < 0.05). The effect declined and was close to precap levels after the policy had been discontinued 12 months after its introduction, when a 1 US$ fixed co-payment per prescription was introduced (Soumerai 1987). Similar results were found in the cohort of people with schizophrenia (Soumerai 1994).

Also in the cohort of people with schizophrenia, an increase in days of admission to state psychiatric hospitals of 17.0% (P value < 0.001) per patient per month was reported. Similarly, the number of visits per patient per month to two community mental health centres increased abruptly by 43.0% and 57.0% (P value < 0.001), respectively, for these health centres, and was sustained throughout the period (Soumerai 1994).

Reimbursement restricted to one antiulcer prescription item with one refill reimbursed at a time versus no restrictions

Setting: 1992, low-income population (Medicaid) in Florida, USA (Cromwell 1999).

Risk of bias: ITS study with no serious limitations.

The policy also restricted high-dose prescription treatment for patients with acute disorders to 60 days of medication.

The reduction in the number of doses reimbursed was 42.7% (95% confidence interval (CI) -50.1% to -35.4%). At one-year follow-up, the reduction was 39.6% (95% CI, -49.0% to -30.3%).

Medicine expenditures by the health insurer for antiulcer treatment dropped immediately (dollars reimbursed) by 37.8% (95% CI -45.1% to -30.5%). At one-year follow-up, the reduction was 32.0% (95% CI -40.7% to -23.3%).

Changes in hospitalisation rates were small and were likely to have occurred by chance. Immediate effects were 7.4% (95% CI -17.1% to 32.0%) for complicated peptic ulcer disease (PUD), -10.0% (95% CI -29.6% to 9.6%) for uncomplicated PUD and 15.6% (95% CI -9.9% to 41.0%) for non-ulcer peptic conditions. At one-year follow-up, the effect was 9.3% (95% CI -24.7% to 43.3%) for complicated PUD; 15.4% (95% CI -11.1% to 49.9%) for uncomplicated PUD; and 0.8% (95% CI -32.3% to 33.9%) for non-ulcer peptic conditions.

Twenty-day minimum resupply period cap for medicines with five or more repeats versus three-day minimum resupply period

Setting: 1994, Pharmaceutical Benefits Scheme (all residents are eligible), Australia (Donnelly 2000).

Risk of bias: ITS study with no serious limitations.

The last of the cap studies included in this review measured the effect on restricting the medicine supply period in Australia. The intended effect of the Australian policy was somewhat different from that of the policies discussed above. This policy was introduced to manage the problem of a large seasonal effect (in December) after previous introduction of a ceiling policy that had resulted in hoarding of medicines after patients had reached the maximum co-payment level. Before the 20-day resupply cap policy was instituted (i.e. a cap on the time allowed until resupply was possible), marked increases in utilisation were observed towards the end of the year.

After its introduction, peak utilisation was decreased in December by 1,150,196 absolute number of prescriptions dispensed (95% CI 708,333 to 1,592,059), which is estimated to be about a 20% relative reduction that appeared to decrease over time (assessed 68 months after the intervention was implemented).

2. Cap with co-insurance and ceiling

Seven studies addressing one intervention met our inclusion criteria. All of them used an ITS/RM study design (Chen 2008b; Farley2010a; Polinski 2012; Schneeweiss 2009; Shrank 2008; Yin 2008; Zhang 2009b). A summary of findings for cap policies is provided in Summary of findings 2, and additional details on each study are presented in Table 11.

Medicare part D is an access to medicines programme in the USA that started in 2006 and targets especially the elderly population. At the time of the studies, the programme consisted of a $32 monthly premium and a $250 deductible, then co-insurance of 25% up to $2250 in total medicine costs, followed by a gap in coverage, during which enrollees pay 100% of the costs of their medications. After enrollees incur $3600 in out-of-pocket expenses, then qualify for catastrophic coverage and pay 5% of medication costs (cited below simply as Medicare part D).

2.1 Medicare part D versus no previous medicine coverage

Setting: 2006, USA (Polinski 2012, Schneeweiss 2009).

Risk of bias: one RM and one ITS study with no serious limitations.

Implementation of Medicare part D for elderly individuals who previously lacked medicine coverage was associated with increased medicine use and reduced out-of-pocket expenses.

One study on the use of antipsychotic medication found that implementation of this policy resulted in an immediate increase of 8007 (95% CI 7078 to 8937) days' supply (per 1000 patients), followed by a decrease of 227 days' supply (95% CI -381 to -73) in each month after Medicare part D implementation. The aggregated result indicated an overall increase of 97% in this indicator (Polinski 2012).

Regarding out-of-pocket expenses, the same study found a 62% reduction in out-of-pocket expenses in 2006. Enrolment in Medicare part D was associated with an immediate $86 (95% CI, -$96 to -$76) decrease in out-of-pocket costs per 30-day supply of medicines, and a $4 (95% CI $3 to $5) increase in out-of-pocket costs per 30-day supply each month thereafter (Polinski 2012).

The other study focused on essential medications (as classified by the study authors) and found that Medicare part D was associated with increased use of those medicines. Higher percentage

increases were found for the generic forms particularly. Out-of-pocket spending was drastically reduced (around 50% reduction) (Schneeweiss 2009).

Important changes were found in the use of all medicines except warfarin in relation to the baseline period. The intervention resulted in a total increase of 22% for statins (> 2.5 million defined daily doses (DDDs)), 11% for clopidogrel (> 154,000 DDDs) and 37% for proton pump inhibitors (PPIs) (> 723,000 DDDs). Generic pravastatin and simvastatin accounted for about 29% of all statins dispensed shortly after their market entry in April and June 2006, respectively. Use of these less costly generics immediately increased by 132,700 daily doses per month following implementation of the policy. As an illustration of this, the generic omeprazole had a 560% increase in its utilisation, representing the highest rate of use of all medicines addressed in this study. In accordance with this result, the highest reduction in out-of-pocket spending was seen with the generic form of omeprazole (-80%). The reduction in out-of-pocket costs for all other medicines ranged from 37% to 67% (Schneeweiss 2009).

The study authors argued, however, that a sizeable proportion of sicker patients reached the coverage gap in the first year, then experienced a drop in use of medicines that they had been using before they reached the coverage gap.

2.2 Medicare part D versus previous coverage of a co-payment medicines programme (known as Medicaid) for low-income elderly people

Setting: 2006, USA (Shrank 2008).

Risk of bias: ITS studies with no serious limitations.

Medicaid is a social healthcare programme that targets low-income families and those with limited resources. Its beneficiaries had heterogenous medicine coverage, in accordance with each state policy, before implementation of Medicare part D.

Shrank 2008 found changes in medicine days covered and out-of-pocket spending for statins, clopidogrel, PPI and warfarin, but not for benzodiazepines. The immediate effect on medicines use, represented by the level change, was an increase of 8801 days' supply (95% CI: -4,301 to 21,912) for statins; 1566 (95% CI:-1,352 to 4,483) for clopidogrel; 5308 (95% CI:-1,769 to 12,385) for PPIs; and 1,653 (95% CI:-798 to 4,105) for warfarin. The slope change, representing the 10-month effect of policy implementation, also showed an increase in use of medicines in terms of days supply: 1397 (95% CI:540 to 3,333) for statins; ; 925 (95% CI:-113 to 1963) for PPIs; and 17 (95% CI:-343 to 376) for warfarin and a decrease of -99 (95% CI:-527 to 329) for clopidogrel. Relevant changes in co-payments occurred with implementation of Medicare part D, resulting in decreased annual cumulative out-of-pocket expenses by $6.14 for PPIs, $6.62 for statins, $10.58 for warfarin and $18.42 for clopidogrel for dual eligibles (Medicaid and Medicare part D).

Benzodiazepines were explicitly excluded from Medicare part D coverage but were potentially covered through Medicaid. For this group of medicines, a large increase in out-of-pocket costs was reported, as well as a slight reduction in their use. As a result of exclusion of benzodiazepines from Medicare part D coverage, the state Medicaid programmes (those that allowed coverage for beneficiaries with Medicaid alone) were required to extend benzodiazepine coverage to dual-eligible beneficiaries.

2.3 Medicare part D versus mixed pharmaceutical coverage

Setting: 2006, USA (Chen 2008b; Yin 2008; Zhang 2009b).

Risk of bias: ITS and RM studies with no serious limitations.

This section presents studies that compare Medicare part D coverage versus different kinds of pharmaceutical previous coverage arrangements. Chen 2008b and Yin 2008 used population data from consumers of large retail chains in the USA, and Zhang 2009b classified its population into four groups: (1) generous employer-subsidised drug coverage that did not change with part D; (2) without previous pharmaceutical coverage; (3) previously covered with quarterly expenditures capped at $150 and tiered co-payments ($8 generic/$20 brand); and finally, (4) previously covered with the same tier co-payments with quarterly expenditures capped at $350.

Yin 2008 evaluated the intervention Medicare part D using data from a big pharmacy chain in the USA. The main outcomes were medication utilisation (measured as pill-days) and out-of-pocket spending. January 2006 to May 2006 was a penalty-free period for Medicare part D enrolment (considered a ramp-up phase). After that, it was necessary to pay a penalty surtax to enrol. During the penalty-free period, average monthly medicine utilisation was increased by 1.1% (95% CI 0.5% to 1.7%; P value = 0.001) and out-of-pocket expenditures were decreased by 8.8% (95% CI 6.6% to 11.0%; P value = 0.001). After this period, average monthly medicine utilisation was increased by 5.9% (95% CI, 5.1% to 6.7%; P value = 0.001) and out-of-pocket expenditures were decreased by 13.1% (95% CI 9.6% to 16.6%; P value = 0.003). Among seniors who enrolled during the penalty-free enrolment period, Medicare part D is estimated to have decreased expenditures by $7.90 monthly average out-of-pocket prescription costs per person (13.4%; P value = 0.001). The postpenalty-free period (June 2006 and April 2007) was characterised by a reduction of $11.10 (20.4%; P value = 0.001). The intervention led to an increase of 5.5 pill-days (quantity of a prescription medicine sufficient for one day of therapy per person) per month (5.9%; P value = 0.001) during the penalty-free period and an increase of 13.7 pill-days during the stable period (16.1%; P value = 0.001).

Another study (Chen 2008b) evaluated the impact of this policy on psychotropic medicine utilisation and the financial burden placed on the elderly in relation to purchase of these drugs. Analysis was based on data from“one of the nation's largest pharmacy chains”, and results were presented separately for antipsychotics, antidepressants and benzodiazepines. With respect to out-of-pocket burden, the proportion of psychotropic prescriptions paid out by seniors was decreased by 18% for antidepressants (from 40% in 2005 to 33% in 2006) and by 21% for antipsychotics (from 28% in 2005 to 22% in 2006). This represents savings of $4.52 per antidepressant prescription and $5.71 per antipsychotic prescription. Unlike antidepressant and antipsychotic medications, benzodiazepines were excluded from the Medicare part D formulary. Therefore, the out-of-pocket share that seniors paid for benzodiazepine prescriptions was increased by 19% (from 63% in 2005 to 75% in 2006) during the same period, which represents a net increase of $2.79 per prescription (P value not reported). Findings therefore were similar to those of Yin 2008.

Finally, Zhang 2009b investigated differences in the impact (out-of-pocket pharmacy spending) of Medicare part D on prior medicine

coverage for the elderly. A reduction in out-of-pocket spending was observed during the first months of policy implementation. However, out-of-pocket payments were increased for some enrollees who had entered the programme during the so-called "coverage gap" period, in which they had reached the cap amount and were responsible for paying all medicine costs themselves. Enrollees stayed in the coverage gap until they have spent $3600 (in 2006); after this, they entered the "catastrophic coverage region", in which they paid only 5% of the cost of medicines. By the end of 2006, out-of-pocket spending had peaked and started to decrease as enrollees reached the ceiling ("catastrophic coverage region") and, therefore, reduced their payment share. Overall, the policy reduced out-of-pocket spending by 13.4% among those without prior coverage (95% CI −17.1% to −9.1%) and by 15.9% among those with prior $150 quarterly caps (95% CI −19.1% to −12.8%).

3. Fixed co-payments

Four interventions in five publications met the inclusion criteria. All of these studies used an ITS design (Hux 1997; Nelson 1984; Reeder 1985; Roblin 2005; Sawyer 1982). A summary of the findings for cap policies is provided in Summary of findings 3, and further details on each study are presented in Table 13.

3.1 Income based: CAD 100 full co-payment, after which patients had to pay CAD 6.11 or CAD 2 (low-income) per prescription versus full pharmaceutical coverage

Before the policy was implemented, elderly people in Ontario Province, Canada, were fully covered by the region's medicines programme. This meant that prescription medicines were provided to that population at no cost to the individual. In May 1996, the government announced an income-graded co-payment scheme, which consisted of a CAD 2 co-payment on each prescription filled for low-income elderly. Higher-income elderly faced a CAD 100 deductible per person per year and a CAD 6.11 co-payment for each subsequent prescription.

Setting: 1996, Ontario medicine benefit programme (all seniors eligible), Canada (Hux 1997).

Risk of bias: ITS study with serious limitations for drug use outcome.

For all classes of medicines studied, the number of prescriptions was decreased, but the quantity per prescription was increased. The overall reduction in the number of prescriptions was 14.2%, and volume (which accounts for numbers of prescriptions and quantity of medicines) was reduced by 6.0% at five months post policy. For “essential medicines”, the reduction in the number of prescriptions ranged from 10.3% to 15.9% (P value not reported). Effects on volume were reported to be statistically not significant, ranging from -1.3% to +2.6%, with the exception of antipsychotics, which had a reduction of 8.7% (P value < 0.05). For all “discretionary medicines”, the reduction in the number of prescriptions ranged from 14.3% to 24.3% (P value not reported). The reduction in volume for most discretionary medicines was statistically significant (P value < 0.05) and ranged from -10.9% to -20.0%, with the exception of sedatives (-4.0%; P value > 0.05). An 11.3% reduction was observed in the number of prescriptions for lipid-lowering (“preventive”) medicines (P value not reported), as well as a 1.7% reduction in volume (P value not reported). Pharmaceutical expenditures by the health insurer decreased by 16.9% (P value not reported).

3.2 USD 0.50 fixed co-payment per prescription versus full medicines coverage

Before the policy change was made, medicines were fully covered in this scheme. Some US states then implemented a USD 0.50 fixed co-payment per prescription for low-income populations.

Setting: 1977, low-income patients (Medicaid) in South Carolina (Nelson 1984; Reeder 1985) and Maryland (Sawyer 1982), USA.

Risk of bias: ITS study with some serious limitations.

One study reported in two publications measured the effect of a USD 0.50 co-payment per prescription in a Medicaid population (Nelson 1984; Reeder 1985). Results were reported as absolute changes in level per person and showed serious limitations regarding drug use outcomes. Overall use of medicines was reduced by 0.3 prescriptions per person (P value < 0.05), which was estimated to be about 12.0% below the value predicted by the preintervention level and slope (Nelson 1984). The effect on individual medicine groups ranged from +0.1 to -0.4 prescriptions per person (Reeder 1985). Medicine expenditures were decreased by USD 2 per person per month (P value < 0.05) and were estimated to be 16.0% below the value predicted by the preintervention level and slope (Nelson 1984). The other study (Sawyer 1982) addressed a similar policy, with the difference that the previous policy had included most over-the-counter medicines in its full medicine coverage. The policy led to a change of 0.1% (95% CI -15.0% to 15.2%) in overall medicine expenditures for the health insurer.

3.3 Increased co-payment versus lower amounts

One of the studies (Roblin 2005) included here considered five managed care organizations (MCOs) in the USA and sought to investigate the effects of increased co-payments on medicine utilisation rates. The groups had heterogeneous co-payment benefits before the intervention, and so the study authors classified the increases into three categories - small ($1 to $6), moderate ($7 to $10) and large (> $10) - and compared utilisation rates with those of a group that had received no increase in co-payment. The other study (Ong 2003) addressed an intervention in Sweden in which the initial co-payment amount was increased from SEK 125 to SEK 160, and the amount for additional medicines from SEK 25 to SEK 60.

Setting: USA (northeast, southeast, midwest, west) (Roblin 2005) and Sweden Ong 2003.

Risk of bias: ITS studies with no serious limitations.

Roblin 2005 evaluated different levels of increase in co-payments and their effects on average daily dose of oral hypoglycaemic medications. Results showed that after the increase, the small increase group ($1 to $6) had a 1% increase (P value = 0.52) in medicine use, and the moderate-increase ($7 to $10) and large-increase (> $10) groups experienced a 6.10% (P value = 0.25) and a 15.97% (P value = 0.01) decrease, respectively. The effect of the large co-payment increase on hypoglycaemic medication use was immediate, resulting in a 3.6% decrease (P value = 0.16) a month after the intervention was implemented.

Ong 2003 addressed antidepressants, anxiolytics and sedatives - all symptomatic medicines hypothesised to have discretionary uses and to be consumed less often when patients faced higher

costs, despite the high burden of related conditions in Swedish society. The effects of the policy were examined separately for men and for women, as the main health conditions addressed in this study (depression, anxiety and sleep disorders) were found to be more prevalent among women than men in Sweden. Women's use of medicines (DDDs per 1000 patients) was temporarily increased immediately preceding the policy by 6618 (P value < 0.01) for antidepressants, by 2861 (P value < 0.01) for anxiolytics and by 8734 (P value < 0.01) for sedatives. However, no sustained changes in use of any of the medicines post policy were reported (figures not reported). Men's use (DDDs per 1000 patients) of all three medicines was increased in the two months before the policy by 2749 (P value < 0.01) for antidepressants, by 3477 (P value < 0.01) for sedatives and by 1759 (P value < 0.01) for anxiolytics. This trend was interrupted for the use of antidepressants (-5275; P value < 0.01) and sedatives (-5838; P value < 0.01) but continued to rise after the policy was in place. No change was reported post policy in prescriptions for anxiolytics (figures not reported). Immediate increases observed directly after implementation of the policy were explained by the study authors as a consequence of stockpiling in response to the co-payment change. However, the study authors pointed out that their analysis was not specific enough to reveal whether this was due to existing or new users.

4. Tier with fixed co-payments

Two publications evaluating two interventions met our inclusion criteria: one CBA (Huskamp 2007) and one ITS (Hartung 2008). A summary of findings for addressed policies is provided in Summary of findings 4, and further details on each study are presented in Table 14.

4.1 Implementation of tier with fixed co-payment versus full medicine coverage

The intervention consisted of implementation of a co-payment for prescription medicines, set at USD 2 for generic and USD 3 for branded medicines. Before this intervention was provided, prescription medicines were covered free of charge. This programme targeted low-income populations in a state in the USA.

Setting: USA, Oregon fee-for-service (FFS) Medicaid programme (Hartung 2008).

Risk of bias: ITS study with no serious limitations.

The objective of this study was to quantify the impact of this policy on medication and health services utilisation overall and among individuals with several common chronic diseases enrolled in Oregon's Medicaid programme. Medicine utilisation was measured as prescriptions dispensed per hundred members per month (PHMPM). Health services utilisation was measured as outpatient office visits, hospitalisations and emergency department (ED) encounters PHMPM. Results show that utilisation of all prescription medicines decreased by 17.2% (95% CI -20.7% to -13.6%; P value < 0.001). No significant trend change was observed from the preintervention to the postintervention period. The impact of the policy differed depending on the medicine class investigated.

Important reductions in the use of all studied classes were observed immediately after the policy was enacted. Diabetes-related medication exhibited a 13.5% (95% CI 18.0% to 9.0%; P value < 0.0001) reduction in utilisation after policy implementation. Medicines dispensed for cardiovascular disease were decreased immediately by 13.1% (95% CI -17.2% to -8.9%; P value < 0.001). Utilisation of medicines for respiratory disease demonstrated an immediate decline of 18.7% (95% CI -23.7% to -13.8; P value < 0.0001), although it returned to normal levels two years after the intervention was provided.

Utilisation of antidepressants and medicines for schizophrenia declined by 19.6% (95% CI -23.5% to -15.6%; P value < 0.0001) and by 12.4% (95% CI -16.5% to -8.4%; P value < 0.0001), respectively, after policy implementation. Reductions were also observed for both mental health medicine classes. For health services utilisation, no immediate segment changes for any medical service outcome were observed after implementation of the policy. A positive trend change in hospitalisations (0.04 encounters PHMPM; 95% CI 0.01 to 0.07; P value = 0.02) was observed after the co-payment policy was implemented; however, an already existing trend change was noted in the prepolicy period (95% CI -0.07 to -0.01; P value = 0.01).

4.2 Three-tier formulary versus two-tier formulary

Setting: USA Medco Health Solutions Inc. (Medco) (Huskamp 2007).

Risk of bias: CBA study with no serious limitations.

This CBA study (Huskamp 2007) evaluated the impact of a shift from two-tier (generic and brand drugs) to three-tier (generic, preferred and non-preferred brand drugs) schemes in four different pharmacy plans for retired people. These shifts were then compared with two different retiree plans that remained in two-tier schemes. The main outcomes were medicine utilisation, expressed as medication possession ratio (MPR), and spending (monthly spending by enrollees). Small or no effects were found for the MPR (from -0.03 to 0.06; P value ≤ 0.05) after adoption of the three-tier formulary. A shift in the distribution of spending from the plan to the enrollee was noted for almost all classes and plans studied in comparison with the two-tier scheme.

5. Ceilings with fixed co-payments

Six interventions in 10 publications met the inclusion criteria, of which eight had an ITS design (Andersson 2006; Caetano 2006; Dormuth 2008; Dormuth 2009; Hynd 2008; Hynd 2009; McManus 1996; Wang 2008b), one used an RM study design (Dormuth 2006) and one was based on a CBA design (Poirier 1998). A summary of findings for cap policies is provided in Summary of findings 5, and additional details on each study are presented in Table 15.

5.1 Income-based fixed co-payment with ceiling

5.1.1 AUD 15 (general population) or AUD 2.50 (elderly) fixed co-payment per prescription with ceiling versus AUD 11 fixed co-payment per prescription with ceiling (general population), full medicine coverage (elderly)

Setting: 1990, general population and elderly patients, Pharmaceutical Benefits Scheme, Australia (McManus 1996).

Risk of bias: ITS study with no serious limitations.

The level of the ceiling was not reported. Use of "essential" medicines was decreased by 816,000 prescriptions (P value < 0.001, 95% CI -1,116,133, to 516,373), estimated at 22.0% below predicted by the preintervention level and slope. Use of "discretionary" medicines was decreased by 758,500 prescriptions (P value < 0.001; 95% CI -901,189 to -615,813), estimated at 27.0% below predicted

by the preintervention level and slope for both groups: the general population and the elderly.

5.1.2 AUD 2.5 fixed co-payment per prescription with ceiling versus full medicine coverage

Setting: 1992, general community and repatriation patients, Pharmaceutical Benefits Scheme (PBS), Australia (McManus 1996).

Risk of bias: ITS study with no serious limitations.

One study measured the effects of increasing a fixed co-payment from no co-payment to AUD 2.5 per prescription for repatriation patients (returned servicemen and women) belonging to the Australian PBS scheme covering approximately 90% of the community (McManus 1996). A ceiling for payments was set, but the level was not reported. Use of "essential" medicines was decreased by 29,500 prescriptions (P value < 0.001; 95% CI -45,812 to-13,287), estimated at 23.0% below predicted by the preintervention level and slope. Use of "discretionary" medicines was decreased by 32,500 prescriptions (P value < 0.001; 95% CI -44,442 to -20,510), estimated at 24.0% below predicted by the preintervention level and slope.

Investigators observed potential stockpiling effects, which may be expected after patients reached the ceiling. However, a strong pattern of seasonality towards the end of each year was shown post policy (McManus 1996), particularly for the repatriation group, and in the use of "essential medicines". Patterns of seasonality (potential hoarding) could also be seen in the time series for the community cohort.

5.2 CAD 2 fixed co-payment per prescription up to a ceiling of CAD 100 versus full medicine coverage

Setting: 1992, elderly patients in Quebec province, Public Health Insurance Medicines Programme (all eligibles), Canada (Poirier 1998).

Risk of bias: CBA study with no serious limitations.

Use of antihypertensives was reduced by 2.3% (P value < 0.05) for low-income patients and by 3.7% (P value < 0.05) for high-income patients at 18-month follow-up. Use of benzodiazepines was reduced by 1.2% (P value < 0.05) for low-income patients and by 1.3% (P value < 0.05) for high-income patients at 18-month follow-up.

5.3 CAD10 (low-income elderly) per prescription for the first 20 prescriptions of the year, and CAD25 (non-low-income elderly) per prescription for the first 11 prescriptions of the year, versus full medicine coverage

Setting: 2002, Canada, British Columbia (BC), PharmaCare Programme (Caetano 2006; Dormuth 2006; Dormuth 2008; Dormuth 2009; Wang 2008b).

Risk of bias: RM and ITS studies with no serious limitations.

One study evaluated the policy as changes in incidence and discontinuation rates (120-day interval with no record of refills) for the use of antihypertensives and statins (Caetano 2006). Although no important changes were found in any of those measures after introduction of the policy, discontinuation rates were increased (P value ≥ 0.05) just before the policy was introduced. Another study (Dormuth 2006) evaluated the effects of the policy on the use of inhaled medications. Measures used included trends in inhaled medication use; time trends in the probability of initiation or cessation of inhaled steroids; and predictors of initiation or cessation of inhaled steroids. For this systematic review, we chose as the main outcome trends in use. Under the policy, use of inhaled medications was decreased by 7.67% at 12 months after implementation of the policy and by 10.14% at 16 months following implementation (for additional data, see "Co-insurance with ceiling" analysis group in Section 6.2 below).

This study evaluated the effects of two subsequent policy changes. Initially, medicines were provided free of charge. This practice was replaced by the ceiling with fixed co-payment scheme described for this analysis group. After a few months, the scheme was changed to a co-insurance with a ceiling scheme. In addition to the outcome measures presented above, several others were reported by the study authors, who presented all results in relation to the second change in this policy (ceiling with co-insurance) compared with the full coverage period. Therefore, as these secondary outcomes were not reanalysed separately, it is impossible to differentiate their effects and to say whether results were related to the first (discussed in this section) or the second policy change.

A second study (Dormuth 2008) evaluated the effects of this policy on emergency department hospitalisations due to chronic obstructive pulmonary disease, asthma or emphysema (CAE), and on physician visits. No increases were observed in any of these measures. A third study (Dormuth 2009) evaluated policy effects on health plan spending by the British Columbia's Ministry of Health in patients over 65 years of age who used inhaled medications for chronic conditions. This study showed an increase of C$1.51 million per year in physician services (95% CI 0.81 to 2.22 million Canadian dollars per year) and a decrease of C$1.93 million per year in spending on inhaled medications (95% CI 0.26 to 3.59 million Canadian dollars per year). However, out-of-pocket spending by patients on those medicines increased by 30% (C$1.70 million per year; 95% CI 1.39 to 2.01) during the same period. Spending on emergency care and hospitalisations did not change. Overall, the Ministry of Health's spending for this health plan increased by C $1.98 million per year (95% CI 0.10 to 4.34), compared with the full coverage baseline period. A fourth study evaluated the impact of this policy on the use of antidepressants (Wang 2008b). Study authors reported a decrease in antidepressant initiation but no trend change in use of these medicines among the elderly after the policy had been implemented.

5.3 Increased co-payment and ceiling amount

Before the intervention was implemented in Sweden, each patient had an annual ceiling value of SEK 1600 and had to pay 50% of the price of all prescribed medicines. The intervention changed the cap amount, increasing it to SEK 1700 and rearranging the co-payment scheme so the patient pays an initial co-payment of SEK 125 and an additional amount per prescription of SEK 25 (Andersson 2006).

Hynd 2008 and Hynd 2009 studied an Australian intervention in which co-payments for Social Security (SS) beneficiaries increased from AUD $3.70 to AUD $4.60, and the ceiling amount from AUD $197.60 to AUD $239.20. Amounts for general beneficiaries changed in the same way. Co-payments rose from AUD $23.10 to AUD $28.60, and the ceiling from AUD $726.80 to AUD $874.90.

Setting: Australia and Sweden (Andersson 2006; Hynd 2008; Hynd 2009).

Risk of bias: ITS study with serious limitations for the cost outcome (Andersson 2006).

Andersson 2006 selected indicator medicines on the basis of the criteria that these should be used widely and sold mainly as outpatient prescriptions. On this basis, researchers selected non-steroidal anti-inflammatory medicines (NSAIDs) and selective serotonin re-uptake inhibitors (SSRIs), which were chosen because they were encompassed by the reimbursement schedule and were subject to co-payment during the whole study period. Medicines for the treatment of selected chronic diseases were free of charge before January 1997. Indicator groups representing this category of medicines were inhibitors of uric acid production for treatment of gout and selective beta-2-adrenoreceptor agonists, a group of bronchodilators. A decrease was noted in total cost in the reimbursement system for pharmaceuticals (2.52% at 12 months; 4.22% at 24 months) and in the volume of medicines prescribed (7.84% at 12 months; 15.05% at 24 months in number of DDDs) for all pharmaceuticals addressed (11 indicator chemical groups were used). However, an increase was observed in the total cost of pharmaceuticals in the reimbursement system. Regarding the medicine volume for SSRIs, a decrease was noted in the cost and volume of acetic acid derivates (NSAIDs) and related substances.

Hynd 2008 analysed 17 subsidised groups of medicines (antiepileptics, antigout treatments, antiparkinson treatments, anxiolytics, atypical antipsychotics, beta-blockers, combination asthma medicines, eye dropsy and glaucoma treatments, hypnotics, insulin, muscle relaxants, non-aspirin antiplatelets, osteoporosis treatments, PPIs, statins and thyroxine) and the effects of the policy on medicine use, as measured by prescription counts. Results were analysed for two groups: general beneficiaries and SS beneficiaries. A change in all medicine groups was noted with the exception of antigout treatments and anxiolytics. Although increases in use were reported for beta-blockers, antipsychotics (statistically significant only for SS beneficiaries) and hypnotics, use decreased for the other groups among both general and SS beneficiaries. For some medicine groups (such as combination asthma medicines, osteoporosis treatments and PPIs), large reductions in medicine use were observed among people in both plans. A large decrease was also observed for non-aspirin antiplatelet medicines among SS beneficiaries only. Overall, the policy change had a larger impact on SS beneficiaries than on general beneficiaries. A second paper (Hynd 2009) narrowed down the groups of medicines addressed and evaluated the impact of the policy on four medicine groups used for chronic disease: asthma medicines, antipsychotics, PPIs and statins. This policy led to a reduction in prescription count of 8% for combination asthma medicines (P value < 0.001), 9% for PPIs (P value < 0.001) and 5% for statins (P value < 0.001). In terms of DDD (defined daily dose)/1000/d, antipsychotics were decreased by 0.4% per month (risk ratio (RR) 0.996, 95% CI 0.993 to 0.999), and combination asthma medicines were decreased by 1.2% per month (RR 0.988, 95% CI 0.979 to 0.998). PPIs were decreased by 13% immediately after policy implementation (RR 0.87, 95% CI 0.79 to 0.96) and by a further 0.5% per month after this time point (RR 0.995, 95% CI 0.989 to 1.001). Finally, statins were decreased by 10% immediately following the rise in co-payments (RR 0.90, 95% CI 0.82 to 0.99), but no change in the monthly trend was noted.

6. Ceiling with co-insurance

Five interventions in nine studies met the inclusion criteria, of which two interventions were analysed in studies with ITS or RM design (Andersson 2006; Blais 2002; Caetano 2006; Dormuth 2006; Dormuth 2008; Dormuth 2009; Ong 2003; Tamblyn 2001; Wang 2008b) and four in studies with RCT design (Newhouse 1993). Several studies reported results on evaluation of the same interventions in the same setting. Results for each intervention are described in the following subsections. A summary of findings for cap policies is provided in Summary of findings 6, and further details on each study are presented in Table 16.

6.1 Income-based co-insurance and ceiling

Setting: 1996, low-income elderly and welfare patients, Quebec Province, Public Health Insurance Medicines Programme (all eligibles), Canada (Blais 2002; Tamblyn 2001).

Risk of bias: RM and ITS studies with no serious limitations.

The following two subsections address two consecutive policy interventions that took place in Quebec Province, Canada.

6.1.1. 25% co-insurance up to a ceiling of CAD 200 versus full medicine coverage

The overall use of “essential” medicines declined by 17.7% (95% CI -14.8% to -20.5%). Within this group of essential medicines, anticonvulsants decreased by 16.2% (95% CI -9.0% to -23.4%); inhaled corticosteroids by 55.6% (95% CI -49.8% to - 64.4%); and neuroleptics by 15.5% (95% CI -9.9% to -21.8%). The overall use of “less essential” medicines was reduced by 19.4% (95% CI -17.4% to -21.4%).

6.1.2. 25% co-insurance up to an income-based ceiling of CAD 200, CAD 500 or CAD 750 versus CAD 2 fixed co-payment per prescription, up to a ceiling of CAD 100

The overall use of “essential” medicines declined by 6.9% (95% CI -5.5% to -8.4%). Within this group of essential medicines, antihypertensives had an immediate reduction of 16.9% (95% CI -12.0% to -21.9%); anticoagulants of 17.2% (95% CI -12.7% to -21.7%); and nitrates of 22.6% (95% CI -17.6% to -27.7%). The overall use of “less essential” medicines was reduced by 14.0% (95% CI -13.0% to -15.0%). Use of benzodiazepines declined by 23.4% (95% CI -17.1% to -29.6%).

6.2 Income-based deductible policy versus fixed co-payment

Setting: 2003, British Columbia, Canada, Fair PharmaCare IBD (Caetano 2006; Dormuth 2006; Dormuth 2008; Dormuth 2009; Wang 2008b).

Risk of bias: RM and ITS studies with no serious limitations.

This intervention consisted of a family deductible (expenses that must be paid out-of-pocket before an insurer will pay any expenses) of 0% to 2% based on family income, and a co-insurance payment of 25% for prescriptions after the deductible was passed, as well as an out-of-pocket ceiling equal to 1.25%, 2% or 3% of income. Previously, the low-income elderly paid C$10 per prescription for the first 20 prescriptions of the year, and non-low-income elderly paid C$25 per prescription for the first 11 prescriptions. All studies cited in this section focused on the same two consecutive policy changes. The ceiling with fixed co-payment intervention

implemented in 2002 is addressed in the 'Ceiling with fixed co-payment' analysis group, in Section 5.3. Results regarding the second change, related to an income-based deductible, are described below.

Caetano 2006 found no important changes in any of the measures of use of statins and antihypertensives, but found that their discontinuation rates increased just before the policy was introduced, implying that this change was not an effect of this intervention, according to the study authors.

Dormuth 2006 evaluated trends in inhaled medication use. Under this policy, use of inhaled medications increased by 3.09% at 12 months after policy implementation and by 3.28% at 14 months. Dormuth 2008 evaluated the effect of this policy on emergency hospitalisations due to chronic obstructive pulmonary disease, asthma or emphysema (CAE), and on physician visits. They observed a 41% increase in emergency hospitalisation for CAE and a 3% increase in physician visits. A fourth study examined health plan spending (Dormuth 2009) and found that insurers' expenditures on medicines were decreased by 26.91%. Additional spending on emergency hospitalisations related to CAE was 6.46 million CAD per year. This additional spending neutralised the savings on medicine expenditures. In addition, physician services were increased by 4.88 million CAD per year (95% CI 3.65 to 6.13) and out-of-pocket expenditures were increased by 59% (5.81 million CAD per year) (95% CI 5.5 to 6.12). All results were related to the 10-month period after policy implementation.

A fifth study (Wang 2008b) found a decrease in the use of antidepressants (5.56% in 12 months, 9.32% in 24 months and 10.86% in 32 months; P value > 0.05).

6.3. Co-insurance for medicines and services with an income-based ceiling

Setting: 1977, patients from six areas of the USA (the RAND health insurance experiment).

Risk of bias: RCT (Newhouse 1993) with serious limitations.

Newhouse 1993 studied four simultaneous interventions; the results are presented below.

6.3.1. 95% co-insurance up to an income-based ceiling of 5%, 10% or 15%, or maximum USD 1000 per year versus full medicine and service coverage

Overall use of prescription medicines was reduced by 33.6% (P value < 0.05), and overall use of over-the-counter medicines by 33.5% (P value = 0.05), as compared with control. Overall prescription medicine expenditures were decreased by 37.6% (P value < 0.05), and over-the counter medicine expenditures by 35.0% (P value > 0.05).

6.3.2. 50% co-insurance up to an income-based ceiling of 5%, 10% or 15%, or maximum USD 1000 per year versus full medicine and service coverage

Overall use of prescription medicines was reduced by 23.2% (P value < 0.05), and over-the-counter medicines by 59.8% (P value < 0.05), as compared with control. Overall prescription medicine expenditures were decreased by 33.6% (P value < 0.05), and over-the-counter medicine expenditures by 58.9% (P value < 0.05).

6.3.3. 25% co-insurance up to an income-based ceiling of 5%, 10% or 15%, or maximum USD 1000 per year versus full medicine and service coverage

Overall use of prescription medicines was reduced by 18.4% (P value < 0.05), and overall use of over-the-counter medicines was reduced by 15.5% (P value > 0.05), as compared with control. Overall prescription medicine expenditures were decreased by 8.3% (P value > 0.05), and over-the-counter expenditures by 26.8% (P value > 0.05).

6.3.4. 95% co-insurance up to a ceiling of USD 150 per person or USD 450 per family per year versus full medicine and service coverage

Inpatient services in this policy were free, but outpatient services were not covered. Overall use of prescription medicines was reduced by 18.6% (P value < 0.05) and over-the-counter medicines by 5.9% (P value > 0.05). Overall prescription medicine expenditures were decreased by 16.3% (P value > 0.05) and over-the-counter medicine expenditures by 6.1% (P value > 0.05).

6.4. Stepwise scale for patient co-payments

For this intervention, patients paid 100% of the price up to SEK 400, 50% of the price between SEK 400 and SEK 1200, 25% of the price between SEK 1200 and SEK 2800 and 10% of the price between SEK 2800 and SEK 3800. The yearly maximum co-payment was SEK 1400. Before this intervention, payments were as follows: maximum SEK 125/160 for one prescription + SEK 25/60 per additional prescription and annual co-payment maximum SEK 1700 (Andersson 2006; Ong 2003).

Setting: 1997, public health insurance system (all eligible), Sweden.

Risk of bias: ITS studies with serious limitations.

For women, immediate increases were reported in the month preceding the policy in use (DDDs per 100 patients) of antidepressants (16,095) (P value < 0.01), anxiolytics (2739) (P value < 0.01) and sedatives (12,201) (P value < 0.01). After the policy had been introduced, a sustained decrease was observed in the use of antidepressants of -21,129 DDDs per 100 patients (P value < 0.01). Use of anxiolytics changed by -3548 DDDs per 100 patients (P value < 0.01). For sedatives, an immediate change of -11,304 was noted, but this was not sustained (Ong 2003).

No sustained effects were observed in use of medicines by men. As in the women's cohort, increases in use of medicines occurred (DDDs per 100 patients) immediately before the policy was in use; use of antidepressants and sedatives changed by 10,474 (P value < 0.01) and 7703 (P value < 0.01) respectively, whereas anxiolytics showed no statistically significant change prepolicy. Post policy. changes were observed in the use of all three medicines, but the effects decayed over time (-4.393, P value < 0.01 for antidepressants; -1600. P value < 0.01 for anxiolytics; -3415, P value < 0.01 for sedatives)) (Ong 2003). After this policy change, with the exception of antidepressants, use of the other classes of drugs was permanently increased or suffered fluctuations for both sexes.

Another study published in 2006 (Andersson 2006) evaluated the same intervention using 11 indicator medicine chemical groups. Our reanalysed results showed that for all pharmaceuticals, a slight decrease in medicine use was evident at the end of the first year (-0.92%). At 24 months, the number of DDDs had increased by

9.85%, and at 29 months after its implementation, an increase of 14.37% was seen in comparison with the period before the intervention. The first year was associated with a slight reduction in costs (-2.31%). At 24 months, costs were 7.56% higher than in the period before the intervention. Results at 29 months show the same trend, with costs 11.38% higher.

6.5. Increased cost sharing for patients on co-insurance with a stepwise scale and associated with a ceiling, versus lower cost sharing for patients on the same scale

Before the intervention, patients paid 100% of the price up to SEK 400, 50% of the price between SEK 400 and SEK 1200, 25% of the price between SEK 1200 and SEK 2800 and 10% of the price between SEK 2800 and SEK 3800. The yearly maximum co-payment was SEK 1400 for pharmaceuticals. The intervention consisted of an increased yearly co-payment maximum (SEK 1800) and adjusted levels within the scale (100% of the price up to SEK 900, 50% of the price between SEK 900 and SEK 1700, 25% of the price between SEK 1700 to SEK 3300 and 10% of the price between SEK 3300 and SEK 4300).

Setting: 1999, public health insurance system (all eligible), Sweden (Andersson 2006).

Risk of bias: ITS study with serious limitations.

Several pharmaceutical groups experienced reductions (P value < 0.01) in cost and volume (number of DDDs). Reductions in level of costs and in volume were observed for acetic acid derivates, antigout preparations and selective beta-2-agonists. For selective serotonin reuptake inhibitors, no changes in medicine cost and volume (number of DDDs) were observed after this intervention. However, a reduction in the expenditure efficiency outcome was expressed as costs/DDD.

DISCUSSION

Summary of main results

Caps

Restricting reimbursement by using a cap may decrease the use of medicines for symptomatic conditions and overall use of medicines. The effect on use of medicines for asymptomatic conditions has not been reported. This intervention may also decrease insurers' expenditures on medicines. Effects on patients' expenditures and on insurers' expenditures on health care have not been reported. Effects on emergency department use, hospitalisation or use of outpatient care are uncertain. No studies that reported the effects of this intervention on health outcomes were found. The certainty of evidence was assessed as low to very low.

The intervention also had the unintended effect of reducing the use of necessary medicines when applied to "essential" medicines, and put extra strain on already vulnerable populations. In one study, this resulted in increased use of healthcare services and deterioration of health in vulnerable populations (Soumerai 1987). Few evaluations were included; the certainty of the evidence was low for cost and use of medicines, and very low for healthcare utilization.

The largest reductions in medicine use were observed in the policies that we judged to be most intensive (i.e. restricting reimbursement to three medicines, including "essential" medicines, per month in New Hampshire (Soumerai 1987; Soumerai 1991; Soumerai 1994) and restricting reimbursement to only one antiulcer medicine with one refill in Florida (Cromwell 1999)) (see Table 10).

Cap policies are expected to have greater effects for multi-medicine users; this was supported by one study that included outcomes on both multi-medicine users and other medicine users (Soumerai 1987). Normally, multi-medicine users are considered less likely to discontinue their medicine use, as they are more likely to be sick and thus more dependent on their medications. Additionally, cohorts of multi-medicine users in this study were of low income; thus patients may have been particularly sensitive to the restriction.

Introducing a restriction on a certain number of prescriptions or medicines is intended to stimulate the patient to prioritise use of the most important medicines. However, use of "essential" and other medicines was reduced substantially. For instance, in New Hampshire, the largest reduction in the actual number of prescriptions was noted for several commonly used "essential" medicines (Soumerai 1987).

A cap on the number of prescriptions or prescription items, but not on volume (the number of doses), may offer a loophole for physicians and consumers to increase the doses prescribed per prescription. Although no direct data on health effects were reported, changes in the use of other healthcare services in a study of vulnerable patients (Soumerai 1994) indicate that some patients had adverse health outcomes requiring emergency department visits and hospitalisations.

Two papers (Soumerai 1987; Soumerai 1994) reported savings in medicine reimbursements but emphasised that even though the policy may have reduced expenditures for health plans, the savings may be low compared with the cost of potential side effects from "essential" medicine discontinuation and increased use of healthcare services among certain vulnerable populations.

Overall, studies addressing cap implementation show that these policies reduced medicine use, even for medicines considered 'essential'. Medicine expenditures for insurers were also reduced, although use of healthcare services tended to increase.

Cap with co-insurance and ceiling

The seven studies assessing the combination of cap, co-insurance and ceiling changes were related to the introduction of Medicare part D in the United States in 2006. This intervention may increase overall use of medicines as well as use of medicines for symptomatic and asymptomatic conditions, and may decrease patient expenditures on medicines. Effects on healthcare expenditures, healthcare utilisation and health outcomes were not reported. The certainty of evidence was assessed as low to very low (for the case of overall medicine use). Overall, impact on both medicine use and expenditures varied in relation to therapeutic class and previous medicine coverage.

It is notable that the benefits of Medicare part D were not distributed evenly throughout the year, as a sizeable proportion of patients reached the coverage gap before year end. This resulted in reductions in the dispensing of previously used essential medications (Schneeweiss 2009).

It is important to highlight that the effects of Medicare part D varied according to previous coverage of participants. For elderly populations who previously had no medicine coverage, implementation of Medicare part D was associated with increased medicine use and reduced out-of-pocket expenses (Polinski 2012; Schneeweiss 2009). For elderly populations who were part of Medicaid as a consequence of low income, implementation of Medicare part D had mixed effects.

Shrank 2008 showed increased use and reduced out-of-pocket spending for statins, clopidogrel, PPI and warfarin, but not for benzodiazepines, which were not included in Medicare part D. These changes in medicine use as well as in out-of-pocket expenses had different impact according to the therapeutic class. For benzodiazepines, the study found decreased use and increased out-of-pocket expenses. The same effect was not seen with other medicines. These findings may be explained by the fact that because Medicare part D did not cover benzodiazepines, its results with this treatment were quite different from those seen with other therapeutic classes.

Fixed co-payments

Introducing a fixed co-payment had an uncertain effect on overall use of medicines; however, it may decrease the use of medicines for symptomatic and asymptomatic conditions. The intervention may slightly decrease insurer expenditures on medicines, but no report has described its effects on patient expenditures and insurer expenditures on health care. No studies were found that reported the effect of this intervention on healthcare utilisation or on health outcomes. Few evaluations were included, and the certainty of the evidence was low to very low.

It is plausible to expect that shifting from full medicine coverage to a co-payment structure would reduce medicine use. However, the magnitude of the amount paid by patients seems low, and the higher value for low-income patients was 2 US$. Ong 2003 also observed these modest effects when evaluating consecutive policy changes in Sweden. Study authors suggested that patients may have valued the medicines more highly than the burden of increased co-payments. This type of behaviour was investigated in a study by Roblin 2005, which addressed three ranges of increased co-payments for retirees in the USA, and found that increases greater than 10 USD resulted in a significant reduction in hypoglycaemic medicine use. However, increases between 1 USD and 10 USD had a small impact on medicine use. It should be noted that these interventions were implemented in high-income countries, where willingness to pay is perhaps less likely to be affected by low fixed co-payment values. This may explain why only a small decrease in medicine use was observed.

Data on medicine use disaggregated by income or other sociodemographic variables were not reported. It is therefore difficult to draw any conclusions on differences in medicine use across such groups. One study evaluated the effects of an income-based policy introduced in Canada, but the effects were reported as aggregated figures for low-income and higher-income groups (Hux 1997). This is unfortunate, as not only might patients from different income groups have reacted differently to a co-payment policy, but these groups received interventions of different intensity.

Hux 1997 examined the impact of fixed co-payments on the use of antipsychotics and found that discontinuation of these medicines led to higher rates of emergency department use and use of other health services in this patient cohort. Study authors note that this group seemed to be particularly vulnerable to the adverse effects of co-payments (Hux 1997), suggesting that people with some chronic diseases might be more highly affected by this mechanism. Reeder 1985 found substantial reductions in psychotherapeutics and other "essential" or important medicines, such as diuretics and cardiovascular medicines, which the authors note are not likely to be overprescribed. Further research on the impact of these co-payments is needed.

Overall, reductions in medicine use and in medicine expenditures may have led to cost savings for insurers. However, as effects on health, healthcare utilisation and patient expenditures were not reported, we do not know what effects discontinuation of medicines may have had on, for example, vulnerable populations or healthcare utilisation.

Different factors may have modified the expected effects of these interventions. The study of the Canadian intervention (Hux 1997), which perhaps was the most intensive of the policies included (CAD 100 initial payment, after which patients paid CAD 6.11), reported that physicians, in an attempt to protect patients from the co-payment, may have changed their prescribing patterns. An increase in volume per prescription for "essential" medicines nearly offset the drop in the number of prescriptions. Similarly, a study from Maryland found that introduction of the patient co-payment led physicians to increase the size of prescriptions as a way of lowering expenditures for patients (Sawyer 1982). In South Carolina, physicians and pharmacists may have exempted patients from the co-payment, which had a small impact (Nelson 1984; Reeder 1985).

Tier with fixed co-payment

Implementation of, or an increase in, tier combined with fixed co-payment may lead to little or no difference in overall use of medicines and in use of medicines for symptomatic and asymptomatic conditions. Effects of this intervention on use of emergency department, hospitalisation and outpatient care are uncertain. No studies were found that reported the effects of the intervention on costs, overall healthcare utilisation or health outcomes. The certainty of evidence was low to very low.

Tiered co-payments are intended to prompt patients to choose more cost-effective medicines or to cover the extra expenses themselves. However, tiered co-payments may also reduce overall medicine use if patients are not willing to substitute other medicines, or if changes in the tier structure also include increased co-payments for generic medicines.

The two studies considered here had major differences in population characteristics and in preintervention policies. Whereas the CBA study evaluated the shift from a two-tier to a three-tier plan for retired elderly in the USA (Huskamp 2007), the ITS study evaluated implementation of cost sharing for people eligible for Medicaid (low-income and younger populations), also in the USA (Hartung 2008). These two differences may explain the differences between studies in observed results. In relation to use of medicines, Hartung 2008 observed an overall reduction of 17% in a Medicaid population, and Huskamp 2007 found no effect or a small effect of three-tier adoption among elderly retirees. Hartung 2008

highlighted that participants were less likely to reduce their use of medicines for chronic conditions, compared with other medicines.

Health services utilisation was assessed by Hartung 2008 only. Over the two-year evaluation period, effects of the policy change on emergency department visits, hospitalisations or office visits are uncertain (very low certainty evidence).

Ceilings with fixed co-payments

This intervention may slightly decrease the overall use of medicines and the use of medicines for symptomatic and asymptomatic conditions. The effect of the intervention on insurer medicine expenditures is uncertain. The intervention may lead to little or no difference in emergency department, hospitalisation and outpatient care. Effects on patient medicine expenditures or on insurer expenditures on health care and health outcomes were not reported. The certainty of evidence was low, except for insurer expenditures on medicines, for which certainty was very low.

Fixed co-payments with a ceiling may slightly reduce the overall use of medicines compared with full medicine coverage. Some variation in effects may be noted across settings.

It is important to consider the nature of the changes in the policies evaluated.

The CAD 2 fixed co-payment with a ceiling in Quebec, Canada, had only a modest effect on medicine utilisation in both income groups and medicine categories (Poirier 1998). The primary explanation for why medicine use was more or less unchanged may be that increased patient co-payments did not exceed patient resources and need for medication, and that the insurer achieved savings through a partial shift of costs to patients. However, investigators state that pharmacists expressed concerns regarding introduction of the co-payment policy, and therefore may have been willing to share some of the burden. Unfortunately no data were reported on this. The study had limitations because no data were reported on the selection criteria or on the comparability of control groups. Also, low- and high-income groups were defined on the basis of postal codes, and the reliability of this is uncertain.

A study examining the co-payment change in Australia in 1990 did not present results separately for the two populations addressed (the general population and the elderly), even though the interventions were quite different. According to the authors' (McManus 1996) classification of medicines, no significant differences were observed between essential and discretionary groups. In 1992 the government expanded the co-payment intervention targeting the elderly to also include repatriation patients, with similar results. Study authors highlighted that one major difference in Australia, compared with other countries in which co-payment has been implemented, is that elderly and repatriation patients received an allowance to compensate for its implementation. Even with this compensation, reductions were considerable in all groups addressed, at around 25%. Nevertheless, as results were not reported by population, it is not possible to ascertain the proportion of this reduction that relates only to the elderly or to general populations.

Five studies (Caetano 2006; Dormuth 2006; Dormuth 2008; Dormuth 2009; Wang 2008b) have evaluated the same intervention that was provided in 2002 in British Columbia, Canada. Three of these studies reported results as medicine use measures. Across different medicine groups, results ranged from no effect to a small decrease in use. The largest reduction was reported by Dormuth 2006 on use of asthma inhalers (10.14%), although a subsequent study found no impact of this on healthcare utilisation (Dormuth 2008). The other two studies, although they reported no important changes, observed reductions in antidepressant initiation (Wang 2008b) and increased discontinuation rates for antihypertensives and statins (Caetano 2006). These results do not support the theory that symptomatic medicines are less sensitive to higher out-of-pocket expenses than are asymptomatic medicines, according to the classification adopted in this review.

In the same setting, insurer spending on hospitalisation and emergency department visits was not importantly changed (Dormuth 2009), which is congruent with the findings of Dormuth 2008. Dormuth 2009 reported an increase in patient expenditures on medicines and physician services alongside a decrease in medicine expenditures by insurers (Dormuth 2009). This policy therefore led to a shift in costs from insurers to patients, as well as to larger expenditures by insurers on physician office visits.

Andersson 2006 observed a small decrease in medicine use in Sweden, but the certainty of this evidence was very low. Impact on medicine expenditures from the insurer perspective was found to be low. The study highlighted that before 1997, prescribed pharmaceuticals and health care were incorporated into a joint reimbursement schedule with one maximum yearly deductible. Investigators hypothesised that increased co-payments for medical services might have had effects on the sales of pharmaceuticals in the period before 1997, as fewer possible prescribing occasions would have arisen if the number of physician visits had decreased. This makes it difficult to separate effects associated with increased co-payment for pharmaceuticals from those associated with increased co-payment for medical services. It is important to consider that the change in co-payment structure was small in magnitude overall, and may not have affected patients' willingness to pay for medicines.

Ceiling with co-insurance

Implementation of, or an increase in, the value of the ceiling combined with co-insurance probably slightly decreases the overall use of, and insurer expenditures on, medicines. It may also decrease the use of medicines for symptomatic conditions, although its effect on the use of medicines for asymptomatic conditions remains uncertain. The intervention may lead to increased emergency department utilisation and hospitalisation, and its effect on outpatient care is uncertain. Effects on patient expenditures or insurer expenditures on health care, and on overall healthcare utilisation and health outcomes, were not reported. The certainty of evidence varied from moderate to very low, depending on the outcome.

Blais 2002 noted that the reduction in medicine use was less prominent with medicines that may be accompanied by discomfort that is quickly perceived by patients. Some factors may have modified the effects of the policies. For example, Blais 2002 reported that the large immediate effect of the policy may have been influenced by a hoarding effect, which could be seen immediately before the policy was implemented.

Tamblyn 2001 stratified index medicines into "essential" and "less essential" groups. The first group consists of medications that

prevent deterioration in health or prolong life and would not likely be prescribed in the absence of a definitive diagnosis, and the second, medicines that can provide relief of symptoms but likely will have no effect on the underlying disease process. With both interventions, larger reductions in the use of "less essential" medicines than "essential" medicines were noted. However, this difference was substantial only for the second intervention. In the same study it was found that low-income patients had the greatest reduction in medicine use, despite the fact that they were subject to a less intensive co-payment.

Dormuth 2008 observed an interesting impact of a ceiling with co-insurance on healthcare utilisation. In this study, the increase in insurer expenditures on healthcare utilisation neutralised the savings on medicine expenditures brought about by implementation of the policy.

Comparison of the four different co-payment plans introduced in the USA (RAND health insurance experiment) showed a dose-response relationship to the intensity of interventions, whereby the greatest effect was found in the 50% and 95% co-insurance groups with income-based ceilings. The RAND experiment may have reflected a more restrictive policy than the other policies evaluated, as the co-insurance and the ceiling also included co-payment on services, not only on medicines. Thus the patient not only had to pay a certain amount per prescription but also had to pay to see the physician to obtain a prescription. It was hypothesised by the study authors that people assigned to less generous insurance for prescription medicines would substitute with over-the-counter products. This was not the case. In fact, the study reported that people with more complete prescription coverage used more of both groups of medicines than those with less coverage. Investigators interpreted this as indicating that better financial access to care appeared to promote rather than substitute over-the-counter medicine use. Differences in use between sites were also observed, suggesting that substitution with self care through over-the-counter medicines occurs more in rural areas, where access to physicians and formal care is poor (Newhouse 1993).

When co-insurance (or fixed co-payment) is combined with a ceiling, the intensity of the policy works on two levels. The size of the co-insurance and the ceiling together will determine how rapidly the patient reaches the maximum contribution level. For example, high co-insurance, as in the 95% RAND co-insurance plan, may make it easier for patients to reach the ceiling. Likewise, a low ceiling may make it more probable that the patient will reach the maximum contribution level. The probability of reaching the ceiling will also depend on the size of other medical expenditures. Those with high medical expenditures will be more likely to reach the ceiling, and the size of the co-insurance may not have been so important for this particular group. This was the case in the RAND health insurance experiment. In other words, if the ceiling is easily reachable, the size of the co-insurance may not matter so much.

None of the studies reported on potential hoarding effects after patients reached the ceiling.

Overall completeness and applicability of evidence

In general, included studies provided insufficient information about context characteristics that might modify the impact of policies being evaluated, particularly information about disposable income or other information that would make it possible to gauge the intensity of the interventions. Other factors that might modify the impact of the policies (see Table 1) were not reported or were not possible to assess because of the wide variation in characteristics of the interventions evaluated and the contexts in which they were evaluated.

Certainty of the evidence

We found one randomised trial, six RM studies and 21 ITS studies, most of which were well designed and implemented. However, for the most part, the certainty of the evidence was low or very low for the comparisons and outcomes that we found, mainly because of study design. Some studies were downgraded because of problems regarding risk of bias, imprecision and publication bias (please see Summary of findings for the main comparison; Summary of findings 2; Summary of findings 3; Summary of findings 4; Summary of findings 5; Summary of findings 6). Few studies reported impact on healthcare utilisation, and none reported health outcomes.

Potential biases in the review process

We identified 21 abstracts of potentially relevant studies for which we were not able to retrieve full-text reports. In addition, it is possible that other cap and co-payment policies have been evaluated and reported only in internal documents, which we were not able to find. However, we found no indication of publication bias, and many of the included studies reported uncertain results.

Agreements and disagreements with other studies or reviews

Three systematic reviews have addressed the effects of cap and co-payment policies: Lexchin 2004b; Polinski 2010; Polinski 2011. However, two included only evaluations of US Medicare part D (Polinski 2010; Polinski 2011). The third included only studies published between 1997 and 2002 (Lexchin 2004b). Although several literature reviews have been published, these were limited in scope or addressed only one group of direct payment policies (Adams 2001; Baker 2008; Freemantle 1996; Gibson 2003; Ginsburg 1973; Gleason 2004; Gross 1994; Haaijer-Ruskamp 2002; Harten 2004; Huttin 1994; Levy 1992; Lexchin 2002; Lyles 1999; Nair 2004; Narine 1997; Reeder 1993; Rice 1994; Rice 2004; Sinnott 2013) or specific settings (Baji 2012a). Thus, our review is more comprehensive and up-to-date than these previous reviews. The main findings of this update are consistent with those of the previous version of this review (Austvoll-Dahlgren 2008).

AUTHORS' CONCLUSIONS

Implications for practice

Introducing or raising direct patient payments for medicines through caps, co-payments, co-insurance or combinations of these was found to reduce the use of both important and unimportant medicines across studies. However, impact was sometimes uncertain and varied from small to moderate relative reductions. Reductions were found among medicines for symptomatic and asymptomatic conditions. These included medicines that were important for treating chronic conditions. Findings suggest that patients may not have prioritised their medicine use when faced with a reimbursement restriction. It is also plausible that patients were not able to afford the increased cost, even though they understood the importance of different types of medicines, and/or

that they prioritised their spending (e.g. for different medicines and other goods, like food) in ways that made sense to them.

It is uncertain whether introducing policies such as a more restrictive cap, which increase direct patient payments for medicines, increases the utilisation of other health services or adversely affects health outcomes. Although the shift of cost from insurers to patients may lead to savings for the insurer in terms of expenditures on medicines, discontinuation of medicines may have had unintended effects on healthcare utilisation. From the insurer perspective, discontinuation of medicines might lead to an increase in other healthcare expenditures. From the patient perspective, discontinuation of medicines might lead to adverse health outcomes. Although some studies found increased hospitalisation and utilisation of emergency departments, for most policies that increased direct patient payments the certainty of the evidence was very low, or few or no studies reported impact on healthcare utilisation. No studies reported health outcomes.

Possible adverse effects on health, indicated by increased healthcare utilisation, were found when a cap or a ceiling with co-insurance was introduced in vulnerable and general populations. Other interventions that increase direct patient payments for medicines might have adversely affected patients through discontinuation of life-sustaining medicines or medicines important for treating chronic conditions, particularly in vulnerable populations.

Because discontinuation of non-essential medicines is less likely to cause harm than discontinuation of essential medicines, direct payments are less likely to cause harm if only non-essential medicines are included, or if exemptions are built in to ensure that patients receive needed medical care. Other interventions, such as education or prior authorisation, might be better suited to address inappropriate use of medicines. If direct payments are used by insurers to keep taxes or premiums down, the insurers should be clear about the rationale for the policy and should consider risks of unintended effects on health and healthcare utilisation.

Many factors might modify the effects of policies that increase direct patient payments for medicines, including the magnitude of the increase in direct payments, the medicines included, the vulnerability of the populations affected, how the changes are implemented and enforced, the availability of exemptions and the information provided to patients and providers. Because of this wide variation in the ways policies that increase direct patient payments have been designed and implemented, and because of the limitations of available studies, the certainty of the evidence is low or very low regarding the impact of caps, co-payments and related policies on rational use of medicines. Studies included in this review provide some indication of the likely effects of some of these policies. However, it is likely that the magnitude of the effects of policies that increase direct patient payments for medicines will be substantially different from that found in the included studies. Consequently, if such policies are implemented, consideration should be given to monitoring and evaluating their impact.

Implications for research

Rigorous evaluation should be considered when direct patient payments for medicines are implemented or intensified. Potential effects on health, healthcare utilisation and administration costs should be measured, preferably by using RCT, RM or ITS designs to minimise risk of bias and to increase the certainty of the evidence. Ways to improve and standardise how the intensity of interventions is reported in such evaluations are needed, particularly in relation to the disposable income of patients or some other metric that allows comparisons across settings and studies.

The co-payment scheme combinations reported here were those identified in the included papers, but other combinations may be in place around the world. Mapping of existing co-payment structures would therefore be relevant to the health system research field. Among the combinations included in this review, those with fewer studies are caps with fixed co-payment and tiers with fixed co-payment.

Studies included in this review were reported from a small number of high-income countries and do not reflect the diversity of contexts worldwide. It is particularly important to evaluate the impact of policies that increase direct patient payments for medicines in low- and middle-income countries because of differences in factors that might modify the impact of these policies, including large vulnerable populations with poor access to health services and few resources. Governments or insurers in these settings have fewer resources to pay for medicines or other health services, thus making direct patient payments attractive or essential for reducing expenditures. All of these factors might increase the risk of adverse effects on healthcare utilisation and health. These aspects are particularly relevant in relation to efforts to achieve universal health coverage. Cost-sharing schemes may be seen as a mechanism that can be included in schemes to achieve universal health coverage in low- and middle-income countries. However, the results presented here suggest that further evaluation of the benefits and adverse effects of such policies in these settings is needed.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Andersson 2006

Methods	ITS
Participants	Swedish population that used any pharmacy in the country
Interventions	Fixed + Cap; Ceiling + Co-insurance; Cap + Co-insurance
Outcomes	Medicine use; cost
Notes	5 consecutive major interventions are addressed. We extracted data from specific data collection formularies (DCFs) for each included intervention, as some topics differ (e.g. bias, outcome information) 3 of the 5 interventions are considered in this review; risk of bias affects the interventions in different ways

Risk of bias

Bias	Authors' judgement	Support for judgement

Andersson 2006 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Not applicable (ITS)
Allocation concealment (selection bias)	Unclear risk	Not applicable (ITS)
Baseline outcome measurement similarity	Unclear risk	Not applicable (ITS)
Baseline characteristics similarity	Unclear risk	Not applicable (ITS)
Protection against contamination	Unclear risk	Not applicable (ITS)
Intervention independent of other changes	High risk	For intervention "C", patent expiration of 1 medicines group is evaluated; therefore, cheaper generic is available, possibly affecting results. For the other interventions included, this risk of bias is classified as low
Shape of the intervention effect pre-specified	Low risk	Point of analysis is the point of the beginning of each intervention
Intervention unlikely to affect data collection	Low risk	Data are collected through the National Corporation of Swedish Pharmacies (Apoteket AB) database, which runs all pharmacies in Sweden since 1971
Incomplete outcome data (attrition bias) All outcomes	High risk	Several months are excluded from analysis as the result of extreme values related to the introduction of new reimbursement schemes. Segments consist of time periods between each of the 5 investigated reforms
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes are objective
Selective reporting (reporting bias)	Low risk	All relevant outcomes in the Methods section are reported in the Results section
Other bias	Low risk	No other important bias is detected in the study

Blais 2002

Methods	ITS
Participants	Setting: Canada, Quebec
Interventions	Ceiling + Co-insurance
Outcomes	Medicine use
Notes	Supported by Grant of the Medical Research Council of Canada, Eli Lilly Canada, Inc., Merck Frosst Canada, Inc., Pfizer Canada, Inc.

Risk of bias

Bias	Authors' judgement	Support for judgement

Blais 2002 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Not applicable (ITS)
Allocation concealment (selection bias)	Unclear risk	Not applicable (ITS)
Baseline outcome measurement similarity	Unclear risk	Not applicable (ITS)
Baseline characteristics similarity	Unclear risk	Not applicable (ITS)
Protection against contamination	Unclear risk	Not applicable (ITS)
Intervention independent of other changes	Low risk	Intervention was independent of other relevant changes
Shape of the intervention effect pre-specified	Low risk	Point analysis is the point of intervention
Intervention unlikely to affect data collection	Low risk	Sources and methods were the same before and after the intervention
Incomplete outcome data (attrition bias) All outcomes	Low risk	No outcome measures are missing
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes are objective
Selective reporting (reporting bias)	Low risk	All relevant outcomes in the Methods section are reported in the Results section
Other bias	Low risk	No other important bias is detected in the study

Caetano 2006

Methods	ITS
Participants	Residents of British Columbia, Vancouver, Canada
Interventions	Ceiling Fixed; Ceiling + Co-insurance
Outcomes	Medicine use
Notes	Paper addresses 2 consecutive interventions

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not applicable (ITS)

Caetano 2006 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Not applicable (ITS)
Baseline outcome measurement similarity	Unclear risk	Not applicable (ITS)
Baseline characteristics similarity	Unclear risk	Not applicable (ITS)
Protection against contamination	Unclear risk	Not applicable (ITS)
Intervention independent of other changes	Low risk	Intervention is independent of other relevant changes
Shape of the intervention effect pre-specified	Low risk	Point analysis is the point of intervention
Intervention unlikely to affect data collection	Low risk	Sources and methods were the same before and after the intervention
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information is provided on missing data
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes are objective
Selective reporting (reporting bias)	Low risk	All relevant outcomes in the Methods section are reported in the Results section
Other bias	Unclear risk	Reason for the effect is unclear, as the change in policy after the 4-month period is not taken into account in the analysis

Chen 2008b

Methods	ITS
Participants	US: Medicare enrollees are users of one of the nation's largest retail pharmacy chains (529 million prescriptions)
Interventions	Cap + Co-insurance + Ceiling (Medicare part D)
Outcomes	Medicine use; cost
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not applicable (ITS)

Chen 2008b *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Not applicable (ITS)
Baseline outcome measurement similarity	Unclear risk	Not applicable (ITS)
Baseline characteristics similarity	Unclear risk	Not applicable (ITS)
Protection against contamination	Unclear risk	Not applicable (ITS)
Intervention independent of other changes	Unclear risk	This is not addressed
Shape of the intervention effect pre-specified	Low risk	Point analysis is the point of intervention
Intervention unlikely to affect data collection	Low risk	Sources and methods were the same before and after the intervention
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	This is not mentioned by study authors
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes are objective
Selective reporting (reporting bias)	Low risk	All relevant outcomes in the Methods section are reported in the Results section
Other bias	High risk	Patients might be covered by Medicaid and Medicare, but these are measured separately

Cromwell 1999

Methods	ITS
Participants	Setting: USA, Florida Medicaid
Interventions	Cap
Outcomes	Medicine use; healthcare utilisation; plan for medicine expenditures
Notes	Supported by National Research Service Award from the Agency for Health Care Policy and Research, and by educational grant from Hoechst Marion Roussel, Inc.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not applicable (ITS)

Cromwell 1999 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Not applicable (ITS)
Baseline outcome measurement similarity	Unclear risk	Not applicable (ITS)
Baseline characteristics similarity	Unclear risk	Not applicable (ITS)
Protection against contamination	Unclear risk	Not applicable (ITS)
Intervention independent of other changes	Unclear risk	Medicine use declined before introduction and announcement of the intervention
Shape of the intervention effect pre-specified	Low risk	Point analysis is the point of intervention
Intervention unlikely to affect data collection	Low risk	Sources and methods were the same before and after the intervention
Incomplete outcome data (attrition bias) All outcomes	Low risk	No outcome data are missing
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes are objective
Selective reporting (reporting bias)	Low risk	All relevant outcomes in the Methods section are reported in the Results section
Other bias	Low risk	No other important bias is detected in the study

Donnelly 2000

Methods	ITS
Participants	Setting: Australia, pharmaceutical benefits scheme
Interventions	Cap
Outcomes	Medicine use
Notes	Source of funding is not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not applicable (ITS)
Allocation concealment (selection bias)	Unclear risk	Not applicable (ITS)

Donnelly 2000 *(Continued)*

Baseline outcome measurement similarity	Unclear risk	Not applicable (ITS)
Baseline characteristics similarity	Unclear risk	Not applicable (ITS)
Protection against contamination	Unclear risk	Not applicable (ITS)
Intervention independent of other changes	Low risk	Intervention is independent of other relevant changes
Shape of the intervention effect pre-specified	Low risk	Point analysis is the point of intervention
Intervention unlikely to affect data collection	Low risk	Sources and methods were the same before and after the intervention
Incomplete outcome data (attrition bias) All outcomes	Low risk	No outcome data are missing
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes are objective
Selective reporting (reporting bias)	Low risk	All relevant outcomes in the Methods section are reported in the Results section
Other bias	Low risk	No other important bias is detected in the study

Dormuth 2006

Methods	RMS
Participants	Canada, British Columbia (BC) PharmaCare Programme
Interventions	Ceiling + Fixed Ceiling + Co-insurance
Outcomes	Medicine use
Notes	Same study as Dormuth 2008, Dormuth 2009 and Wang 2008b 1 of the co-authors received research grants from Pfizer, Inc. The other study authors report no competing interests

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not applicable (RMS)

Dormuth 2006 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Not applicable (RMS)
Baseline outcome measurement similarity	Unclear risk	Not applicable (RMS)
Baseline characteristics similarity	Unclear risk	Not applicable (RMS)
Protection against contamination	Unclear risk	Not applicable (RMS)
Intervention independent of other changes	High risk	Long period (1997-2004): Although some factors were controlled (new medicines in the market and changes in guideline), other aspects such as number of medical care appointments or total potential medical appointment offers may have influenced outcomes measured
Shape of the intervention effect pre-specified	Low risk	Point analysis is the point of intervention
Intervention unlikely to affect data collection	Low risk	Sources and methods were the same before and after the intervention
Incomplete outcome data (attrition bias) All outcomes	Low risk	No outcome data are missing
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes are objective
Selective reporting (reporting bias)	Low risk	All relevant outcomes in the Methods section are reported in the Results section
Other bias	Low risk	No other important bias is detected in the study

Dormuth 2008

Methods	RMS
Participants	Canada, British Columbia (BC) PharmaCare Programme
Interventions	Ceiling + Fixed Ceiling + Co-insurance
Outcomes	Healthcare utilisation
Notes	Although a CRMS, control group is not considered as numbers of control sites are not sufficient Same study as Dormuth 2006, Dormuth 2009 and Wang 2008b 1 of the co-authors received research grants from Pfizer, Inc. The other study authors report no competing interests

Risk of bias

Dormuth 2008 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not applicable (RMS)
Allocation concealment (selection bias)	Unclear risk	Not applicable (RMS)
Baseline outcome measurement similarity	Unclear risk	Not applicable (RMS)
Baseline characteristics similarity	Unclear risk	Not applicable (RMS)
Protection against contamination	Unclear risk	Not applicable (RMS)
Intervention independent of other changes	High risk	As a result of sequential implementation of policy changes in British Columbia, it is difficult to estimate the effect of a direct change from full coverage to an income-based deductible policy
Shape of the intervention effect pre-specified	Low risk	Point analysis is the point of intervention
Intervention unlikely to affect data collection	Low risk	Sources and methods were the same before and after the intervention
Incomplete outcome data (attrition bias) All outcomes	Low risk	No outcome data are missing
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes are objective
Selective reporting (reporting bias)	Low risk	All relevant outcomes in the Methods section are reported in the Results section
Other bias	Low risk	No other important bias is detected in the study

Dormuth 2009

Methods	ITS
Participants	Canada, British Columbia (BC) PharmaCare Programme
Interventions	Ceiling + Fixed Ceiling + Co-insurance
Outcomes	Cost
Notes	2 consecutive interventions are addressed Older patients with asthma or chronic obstructive pulmonary disease are addressed in the paper

Dormuth 2009 *(Continued)*

Same study as Dormuth 2006, Dormuth 2008 and Wang 2008b

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not applicable (ITS)
Allocation concealment (selection bias)	Unclear risk	Not applicable (ITS)
Baseline outcome measurement similarity	Unclear risk	Not applicable (ITS)
Baseline characteristics similarity	Unclear risk	Not applicable (ITS)
Protection against contamination	Unclear risk	Not applicable (ITS)
Intervention independent of other changes	High risk	The Ministry of Health increased its physician and hospital spending in response to the impact of policy changes
Shape of the intervention effect pre-specified	Low risk	Point analysis is the point of intervention
Intervention unlikely to affect data collection	Low risk	Sources and methods were the same before and after the intervention
Incomplete outcome data (attrition bias) All outcomes	Low risk	No outcome data are missing
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes are objective
Selective reporting (reporting bias)	Low risk	All relevant outcomes in the Methods section are reported in the Results section
Other bias	Low risk	No other important bias is detected in the study

Hartung 2008

Methods	ITS
Participants	USA Oregon fee-for service (FFS) Medicaid programme
Interventions	Tier + Fixed
Outcomes	Medicine use; healthcare utilisation
Notes	Some co-authors were full-time employees of Medco Health Solutions when the research was initiated

Hartung 2008 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not applicable (ITS)
Allocation concealment (selection bias)	Unclear risk	Not applicable (ITS)
Baseline outcome measurement similarity	Unclear risk	Not applicable (ITS)
Baseline characteristics similarity	Unclear risk	Not applicable (ITS)
Protection against contamination	Unclear risk	Not applicable (ITS)
Intervention independent of other changes	Low risk	Intervention is independent of other relevant changes
Shape of the intervention effect pre-specified	Low risk	Point analysis is the point of intervention
Intervention unlikely to affect data collection	Low risk	Sources and methods were the same before and after the intervention
Incomplete outcome data (attrition bias) All outcomes	Low risk	No outcome data are missing
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes are objective
Selective reporting (reporting bias)	Low risk	All relevant outcomes in the Methods section are reported in the Results section
Other bias	High risk	Study authors do not report the chance of participants having other financing sources for medicines

Huskamp 2007

Methods	CBA
Participants	USA Medco Health Solutions Inc. (Medco), a large pharmacy benefits manager (PBM)
Interventions	Tier + Fixed
Outcomes	Medicine use
Notes	4 consecutive interventions are addressed in the same paper Some co-authors were full-time employees of Medco Health Solutions when the research was initiated

Huskamp 2007 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	CBA study (no randomisation)
Allocation concealment (selection bias)	High risk	CBA study (no concealment of allocation)
Baseline outcome measurement similarity	High risk	Outcome measures at baseline are not reported by study authors
Baseline characteristics similarity	Low risk	Baseline characteristics of intervention and control groups are similar
Protection against contamination	Low risk	Participants were elderly retirees from different enterprises
Intervention independent of other changes	Unclear risk	Not applicable (CBA)
Shape of the intervention effect pre-specified	Unclear risk	Not applicable (CBA)
Intervention unlikely to affect data collection	Unclear risk	Not applicable (CBA)
Incomplete outcome data (attrition bias) All outcomes	Low risk	No outcome data are missing
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes are objective
Selective reporting (reporting bias)	Low risk	All relevant outcomes in the Methods section are reported in the Results section
Other bias	Low risk	No other important bias is detected in the study

Hux 1997

Methods	ITS
Participants	Canada, Ontario Drug Benefit Programme
Interventions	Fixed co-payment
Outcomes	Medicine use; plan for medicine expenditures
Notes	Source of funding is not reported

Risk of bias

Hux 1997 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not applicable (ITS)
Allocation concealment (selection bias)	Unclear risk	Not applicable (ITS)
Baseline outcome measurement similarity	Unclear risk	Not applicable (ITS)
Baseline characteristics similarity	Unclear risk	Not applicable (ITS)
Protection against contamination	Unclear risk	Not applicable (ITS)
Intervention independent of other changes	Low risk	Intervention is independent of other relevant changes.
Shape of the intervention effect pre-specified	Low risk	Point analysis is the point of intervention
Intervention unlikely to affect data collection	Low risk	Sources and methods were the same before and after the intervention
Incomplete outcome data (attrition bias) All outcomes	High risk	Low- and high-income policies are not differentiated in the outcome
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes are objective
Selective reporting (reporting bias)	Low risk	All relevant outcomes in the Methods section are reported in the Results section
Other bias	Low risk	No other important bias is detected in the study

Hynd 2008

Methods	ITS
Participants	Australian Pharmaceutical Benefits Scheme (PBS) enrollees
Interventions	Ceiling + Fixed
Outcomes	Medicine use
Notes	Same study as Hynd 2009

Risk of bias

Bias	Authors' judgement	Support for judgement

Hynd 2008 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Not applicable (ITS)
Allocation concealment (selection bias)	Unclear risk	Not applicable (ITS)
Baseline outcome measurement similarity	Unclear risk	Not applicable (ITS)
Baseline characteristics similarity	Unclear risk	Not applicable (ITS)
Protection against contamination	Unclear risk	Not applicable (ITS)
Intervention independent of other changes	Low risk	No confounding variables/historic events are reported
Shape of the intervention effect pre-specified	Low risk	Point analysis is the point of intervention
Intervention unlikely to affect data collection	Low risk	Sources and methods were the same before and after the intervention
Incomplete outcome data (attrition bias) All outcomes	Low risk	No outcome data are missing
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes are objective
Selective reporting (reporting bias)	Low risk	All relevant outcomes in the Methods section are reported in the Results section
Other bias	Low risk	No other important bias is detected in the study

Hynd 2009

Methods	ITS
Participants	Australian Pharmaceutical Benefits Scheme (PBS) enrollees
Interventions	Ceiling + Fixed
Outcomes	Medicine use
Notes	Same study as Hynd 2008

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not applicable (ITS)

Hynd 2009 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Not applicable (ITS)
Baseline outcome measurement similarity	Unclear risk	Not applicable (ITS)
Baseline characteristics similarity	Unclear risk	Not applicable (ITS)
Protection against contamination	Unclear risk	Not applicable (ITS)
Intervention independent of other changes	Unclear risk	Not mentioned by study authors, but it is a long period (7 years). Intervener is very unlikely over such a long period
Shape of the intervention effect pre-specified	Low risk	In 3 of the 4 categories examined, prescription counts are significantly lower following the increase in co-payment thresholds. Study authors do give a reasonable explanation
Intervention unlikely to affect data collection	Low risk	Sources and methods were the same before and after the intervention
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Missing data are not mentioned
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All relevant outcomes in the Methods section are reported in the Results section
Selective reporting (reporting bias)	Low risk	No other important bias is detected in the study
Other bias	High risk	Definitions of the 3 beneficiaries groups analysed are not clear

McManus 1996

Methods	ITS
Participants	Australia, pharmaceutical benefits scheme
Interventions	Ceiling + Fixed
Outcomes	Medicine use
Notes	Source of funding is not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not applicable (ITS)

McManus 1996 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Not applicable (ITS)
Baseline outcome measurement similarity	Unclear risk	Not applicable (ITS)
Baseline characteristics similarity	Unclear risk	Not applicable (ITS)
Protection against contamination	Unclear risk	Not applicable (ITS)
Intervention independent of other changes	Low risk	Intervention is independent of other relevant changes
Shape of the intervention effect pre-specified	Low risk	Point analysis is the point of intervention
Intervention unlikely to affect data collection	Low risk	Sources and methods were the same before and after the intervention
Incomplete outcome data (attrition bias) All outcomes	High risk	Community and elderly/social welfare policies are not differentiated in the outcomes
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes are objective
Selective reporting (reporting bias)	Low risk	All relevant outcomes in the Methods section are reported in the Results section
Other bias	Low risk	No other important bias is detected in the study

Nelson 1984

Methods	ITS
Participants	USA: South Carolina and Tennessee Medicaid
Interventions	Fixed co-payment
Outcomes	Medicine use; cost
Notes	Supported by Health Care Financing Administration (HCFA) grant

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not applicable (ITS)
Allocation concealment (selection bias)	Unclear risk	Not applicable (ITS)

Nelson 1984 *(Continued)*

Baseline outcome measurement similarity	Unclear risk	Not applicable (ITS)
Baseline characteristics similarity	Unclear risk	Not applicable (ITS)
Protection against contamination	Unclear risk	Not applicable (ITS)
Intervention independent of other changes	Low risk	Intervention is independent of other relevant changes
Shape of the intervention effect pre-specified	Low risk	Point analysis is the point of intervention
Intervention unlikely to affect data collection	Low risk	Sources and methods were the same before and after the intervention
Incomplete outcome data (attrition bias) All outcomes	Low risk	No outcome data are missing
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes are objective
Selective reporting (reporting bias)	Low risk	All relevant outcomes in the Methods section are reported in the Results section
Other bias	Low risk	Loss to follow-up at 3 years post intervention

Newhouse 1993

Methods	RCT
Participants	USA: Dayton, Seattle, Fitchburg, Franklin, Charleston, Georgetown
Interventions	Ceiling + Co-insurance
Outcomes	Medicine use; cost
Notes	Health Insurance Study grant from the US Department of Health and Social Services, Washington, DC

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random sequence generation is described and adequate
Allocation concealment (selection bias)	Low risk	Allocation of concealment is adequately done
Baseline outcome measurement similarity	Low risk	Outcomes are measured before the intervention, and no important differences are detected among groups

Newhouse 1993 *(Continued)*

Baseline characteristics similarity	Low risk	Baseline characteristics of intervention and control groups are similar
Protection against contamination	Low risk	It is unlikely that the control group received the intervention
Intervention independent of other changes	Unclear risk	Not applicable (RCT)
Shape of the intervention effect pre-specified	Unclear risk	Not applicable (RCT)
Intervention unlikely to affect data collection	Unclear risk	Not applicable (RCT)
Incomplete outcome data (attrition bias) All outcomes	Low risk	No outcome data are missing
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes are objective
Selective reporting (reporting bias)	Low risk	All relevant outcomes in the Methods section are reported in the Results section
Other bias	High risk	Only 4 out of 6 study sites are included in the analysis

Ong 2003

Methods	ITS
Participants	Sweden, Public health insurance
Interventions	Ceiling + Co-insurance
Outcomes	Medicine use
Notes	Source of funding is not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not applicable (ITS)
Allocation concealment (selection bias)	Unclear risk	Not applicable (ITS)
Baseline outcome measurement similarity	Unclear risk	Not applicable (ITS)
Baseline characteristics similarity	Unclear risk	Not applicable (ITS)

Ong 2003 *(Continued)*

Protection against contamination	Unclear risk	Not applicable (ITS)
Intervention independent of other changes	Low risk	Intervention is independent of other relevant changes
Shape of the intervention effect pre-specified	Low risk	Point analysis is the point of intervention
Intervention unlikely to affect data collection	Low risk	Sources and methods were the same before and after the intervention
Incomplete outcome data (attrition bias) All outcomes	Low risk	No outcome data are missing
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes are objective
Selective reporting (reporting bias)	Low risk	All relevant outcomes in the Methods section are reported in the Results section
Other bias	Low risk	No other important bias is detected in the study

Poirier 1998

Methods	CBA
Participants	Canada, Quebec, Quebec drug programme
Interventions	Ceiling + Fixed
Outcomes	Medicine use
Notes	Supported by Règie de l'Assurance du Québec and Seniors Independence Research Program (SIRP), Health Canada

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	CBA study (no randomisation)
Allocation concealment (selection bias)	High risk	CBA study (no concealment of allocation)
Baseline outcome measurement similarity	Low risk	Outcomes are measured before the intervention, and no important differences are detected among groups
Baseline characteristics similarity	High risk	No information is reported on how the control group was selected, or if experimental and control groups are comparable

Poirier 1998 *(Continued)*

Protection against contamination	High risk	Not reported
Intervention independent of other changes	Unclear risk	Not applicable (CBA)
Shape of the intervention effect pre-specified	Unclear risk	Not applicable (CBA)
Intervention unlikely to affect data collection	Unclear risk	Not applicable (CBA)
Incomplete outcome data (attrition bias) All outcomes	Low risk	No outcome data are missing
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes are objective
Selective reporting (reporting bias)	Low risk	All relevant outcomes in the Methods section are reported in the Results section
Other bias	Low risk	No other important bias is detected in the study

Polinski 2012

Methods	IRMS but treated as ITS
Participants	USA Medicare part D
Interventions	Cap + Co-insurance + Ceiling (Medicare part D)
Outcomes	Medicine use; cost
Notes	One of the study authors was a consultant to Buccaneer Computer Systems and Service, Inc., on a contract from the Centers for Medicare and Medicaid Services. Within the previous 5 years, his spouse was employed by DePuy Orthopaedics, a subsidiary of Johnson & Johnson

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not applicable (ITS)
Allocation concealment (selection bias)	Unclear risk	Not applicable (ITS)
Baseline outcome measurement similarity	Unclear risk	Not applicable (ITS)

Polinski 2012 *(Continued)*

Baseline characteristics similarity	Unclear risk	Not applicable (ITS)
Protection against contamination	Unclear risk	Not applicable (ITS)
Intervention independent of other changes	Low risk	Intervention is independent of other relevant changes
Shape of the intervention effect pre-specified	Low risk	Point analysis is the point of intervention
Intervention unlikely to affect data collection	Low risk	Sources and methods were the same before and after the intervention
Incomplete outcome data (attrition bias) All outcomes	Low risk	No outcome data are missing
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes are objective
Selective reporting (reporting bias)	Low risk	All relevant outcomes in the Methods section are reported in the Results section
Other bias	Low risk	No other important bias is detected in the study

Reeder 1985

Methods	ITS
Participants	USA, South Carolina and Tennessee Medicaid
Interventions	Fixed co-payment
Outcomes	Medicine use; cost
Notes	Supported by HCFA grant

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not applicable (ITS)
Allocation concealment (selection bias)	Unclear risk	Not applicable (ITS)
Baseline outcome measurement similarity	Unclear risk	Not applicable (ITS)
Baseline characteristics similarity	Unclear risk	Not applicable (ITS)

Reeder 1985 *(Continued)*

Protection against contamination	Unclear risk	Not applicable (ITS)
Intervention independent of other changes	Low risk	Intervention is independent of other relevant changes
Shape of the intervention effect pre-specified	Low risk	Point analysis is the point of intervention
Intervention unlikely to affect data collection	Low risk	Sources and methods were the same before and after the intervention
Incomplete outcome data (attrition bias) All outcomes	Low risk	No outcome data are missing
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes are objective
Selective reporting (reporting bias)	Low risk	All relevant outcomes in the Methods section are reported in the Results section
Other bias	High risk	Loss to follow-up at 3 years post intervention

Roblin 2005

Methods	CRMS, but treated as an ITS
Participants	USA (northeast, southeast, midwest, west) through a mix of individual, commercial and Medicare plans
Interventions	Fixed
Outcomes	Medicine use
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not applicable (treated as ITS)
Allocation concealment (selection bias)	Unclear risk	Not applicable (treated as ITS)
Baseline outcome measurement similarity	Unclear risk	Not applicable (treated as ITS)
Baseline characteristics similarity	Unclear risk	Not applicable (treated as ITS)
Protection against contamination	Unclear risk	Not applicable (treated as ITS)

Roblin 2005 *(Continued)*

Intervention independent of other changes	Low risk	Intervention is independent of other relevant changes
Shape of the intervention effect pre-specified	Low risk	Point analysis is the point of intervention
Intervention unlikely to affect data collection	Low risk	Sources and methods were the same before and after the intervention
Incomplete outcome data (attrition bias) All outcomes	Low risk	No outcome data are missing
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes are objective
Selective reporting (reporting bias)	Unclear risk	Some outcomes are missing but do not seem to be important
Other bias	Low risk	No other important bias is detected in the study

Sawyer 1982

Methods	ITS
Participants	USA, Maryland, Medicaid
Interventions	Fixed + Co-payment
Outcomes	Cost
Notes	Source of funding is not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not applicable (ITS)
Allocation concealment (selection bias)	Unclear risk	Not applicable (ITS)
Baseline outcome measurement similarity	Unclear risk	Not applicable (ITS)
Baseline characteristics similarity	Unclear risk	Not applicable (ITS)
Protection against contamination	Unclear risk	Not applicable (ITS)
Intervention independent of other changes	High risk	Reimbursement changes are implemented simultaneously

Sawyer 1982 *(Continued)*

Shape of the intervention effect pre-specified	Low risk	Point analysis is the point of intervention
Intervention unlikely to affect data collection	Low risk	Sources and methods were the same before and after the intervention
Incomplete outcome data (attrition bias) All outcomes	Low risk	No outcome data are missing
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes are objective
Selective reporting (reporting bias)	Low risk	All relevant outcomes in the Methods section are reported in the Results section
Other bias	Low risk	No other important bias is detected in the study

Schneeweiss 2009

Methods	RMS
Participants	USA; 3 pharmacy chains (that operate across the whole country)
Interventions	Cap + Co-insurance + Ceiling (Medicare part D)
Outcomes	Medicine use; cost
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not applicable (RMS)
Allocation concealment (selection bias)	Unclear risk	Not applicable (RMS)
Baseline outcome measurement similarity	Unclear risk	Not applicable (RMS)
Baseline characteristics similarity	Unclear risk	Not applicable (RMS)
Protection against contamination	Unclear risk	Not applicable (RMS)
Intervention independent of other changes	Low risk	Intervention is independent of other relevant changes
Shape of the intervention effect pre-specified	Low risk	Point analysis is the point of intervention

Schneeweiss 2009 *(Continued)*

Intervention unlikely to affect data collection	Low risk	Sources and methods were the same before and after the intervention
Incomplete outcome data (attrition bias) All outcomes	Low risk	No outcome data are missing
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes are objective
Selective reporting (reporting bias)	Low risk	All relevant outcomes in the Methods section are reported in the Results section
Other bias	Low risk	No other important bias is detected in the study

Shrank 2008

Methods	ITS
Participants	USA; dual eligible Medicare part D and Medicaid
Interventions	Cap + Co-insurance + Ceiling (Medicare part D)
Outcomes	Medicine use; cost
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not applicable (ITS)
Allocation concealment (selection bias)	Unclear risk	Not applicable (ITS)
Baseline outcome measurement similarity	Unclear risk	Not applicable (ITS)
Baseline characteristics similarity	Unclear risk	Not applicable (ITS)
Protection against contamination	Unclear risk	Not applicable (ITS)
Intervention independent of other changes	Unclear risk	It is not clear if any policy exists at state level that could affect the results; study authors provide no info
Shape of the intervention effect pre-specified	Low risk	Point analysis is the point of intervention
Intervention unlikely to affect data collection	Low risk	Sources and methods were the same before and after the intervention

Shrank 2008 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	No outcome data are missing
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes are objective
Selective reporting (reporting bias)	Low risk	All relevant outcomes in the Methods section are reported in the Results section
Other bias	Low risk	No other important bias is detected in the study

Soumerai 1987

Methods	RMS
Participants	USA, New Hampshire Medicaid
Interventions	Cap
Outcomes	Medicine use; cost
Notes	Supported by grants from the Agency for Healthcare Policy and Research, Department of Health and Human Services/The John A. Hartford Foundation/The National Institute on Aging

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not applicable (RMS)
Allocation concealment (selection bias)	Unclear risk	Not applicable (RMS)
Baseline outcome measurement similarity	Unclear risk	No comparison group is considered
Baseline characteristics similarity	Unclear risk	Not applicable (RMS)
Protection against contamination	Unclear risk	Not applicable (RMS)
Intervention independent of other changes	Low risk	Intervention is independent of other relevant changes
Shape of the intervention effect pre-specified	Low risk	Point analysis is the point of intervention
Intervention unlikely to affect data collection	Low risk	Sources and methods were the same before and after the intervention

Soumerai 1987 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	No outcome data are missing
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes are objective
Selective reporting (reporting bias)	Low risk	All relevant outcomes in the Methods section are reported in the Results section
Other bias	Low risk	Patients could bypass easily the monthly 3-drug limit cap for the first intervention because each time they could fill for 3 months; nevertheless this is controlled in the study

Soumerai 1991

Methods	ITS
Participants	USA, New Hampshire Medicaid
Interventions	Cap
Outcomes	Medicine use; healthcare utilisation; cost
Notes	Supported by grants from the Agency for Healthcare Policy and Research, Department of Health and Human Services/The John A. Hartford Foundation/The National Institute on Aging

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not applicable (ITS)
Allocation concealment (selection bias)	Unclear risk	Not applicable (ITS)
Baseline outcome measurement similarity	Unclear risk	Not applicable (ITS)
Baseline characteristics similarity	Unclear risk	Not applicable (ITS)
Protection against contamination	Unclear risk	Not applicable (ITS)
Intervention independent of other changes	Low risk	Intervention is independent of other relevant changes

Soumerai 1991 *(Continued)*

Shape of the intervention effect pre-specified	Low risk	Point analysis is the point of intervention
Intervention unlikely to affect data collection	Low risk	Sources and methods were the same before and after the intervention
Incomplete outcome data (attrition bias) All outcomes	High risk	"During the follow-up period, similar proportions of patients (35 percent in New Hampshire and 28 percent in New Jersey) died or left the Medicaid program for other reasons"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes are objective
Selective reporting (reporting bias)	Low risk	All relevant outcomes in the Methods section are reported in the Results section
Other bias	Low risk	Patients could bypass easily the monthly 3-drug limit cap for the first intervention because each time they could fill for 3 months; nevertheless this is controlled in the study

Soumerai 1994

Methods	RMS
Participants	USA, New Hampshire Medicaid
Interventions	Cap
Outcomes	Medicine use; healthcare utilisation; cost
Notes	Supported by grants from the Agency for Healthcare Policy and Research, Department of Health and Human Services/The John A. Hartford Foundation/The National Institute on Aging

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not applicable (RMS)
Allocation concealment (selection bias)	Unclear risk	Not applicable (RMS)
Baseline outcome measurement similarity	Unclear risk	Not applicable (RMS)
Baseline characteristics similarity	Unclear risk	Not applicable (RMS)

Soumerai 1994 *(Continued)*

Protection against contamination	Unclear risk	Not applicable (RMS)
Intervention independent of other changes	Low risk	Intervention is independent of other relevant changes
Shape of the intervention effect pre-specified	Low risk	Point analysis is the point of intervention
Intervention unlikely to affect data collection	Low risk	Sources and methods were the same before and after the intervention
Incomplete outcome data (attrition bias) All outcomes	Low risk	Loss of follow-up less than 8% during the whole period of study. Futhermore, this loss was compensated by including in the denominator only the number of participants actively enrolled and each monthly rate
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes are objective
Selective reporting (reporting bias)	Low risk	All relevant outcomes in the Methods section are reported in the Results section
Other bias	Low risk	Patients could bypass easily the monthly 3-drug limit cap for the first intervention because each time they could fill for 3 months; nevertheless this is controlled in the study

Tamblyn 2001

Methods	RMS
Participants	Canada, Quebec, Quebec health insurance programme (RAMQ)
Interventions	Ceiling + Co-insurance
Outcomes	Medicine use
Notes	Supported by the Ministry of Health in Quebec and the Règie de l'assurance maladie du Québec, Ministere de la Santé et des Services Sociaux, the Medical Research Council, the National Research Development Program

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not applicable (RMS)
Allocation concealment (selection bias)	Unclear risk	Not applicable (RMS)
Baseline outcome measurement similarity	Unclear risk	Not applicable (RMS)

Tamblyn 2001 *(Continued)*

Baseline characteristics similarity	Unclear risk	Not applicable (RMS)
Protection against contamination	Unclear risk	Not applicable (RMS)
Intervention independent of other changes	Low risk	Intervention is independent of other relevant changes
Shape of the intervention effect pre-specified	Low risk	Point analysis is the point of intervention
Intervention unlikely to affect data collection	Low risk	Sources and methods were the same before and after the intervention
Incomplete outcome data (attrition bias) All outcomes	Low risk	No outcome data are missing
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes are objective
Selective reporting (reporting bias)	Low risk	All relevant outcomes in the Methods section are reported in the Results section
Other bias	Low risk	No other important bias is detected in the study

Wang 2008b

Methods	ITS
Participants	Canada, British Columbia (BC) PharmaCare Programme
Interventions	Ceiling + Fixed Ceiling + Co-insurance
Outcomes	Medicines use
Notes	One of the co-authors received research grants from Pfizer, Inc. The other study authors report no competing interests Same study as Dormuth 2006, Dormuth 2008 and Dormuth 2009

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not applicable (ITS)
Allocation concealment (selection bias)	Unclear risk	Not applicable (ITS)

Wang 2008b *(Continued)*

Baseline outcome measurement similarity	Unclear risk	Not applicable (ITS)
Baseline characteristics similarity	Unclear risk	Not applicable (ITS)
Protection against contamination	Unclear risk	Not applicable (ITS)
Intervention independent of other changes	High risk	As a result of sequential implementation of policy changes in British Columbia, it is difficult to estimate the effect of a direct change from full coverage to an income-based deductible policy
Shape of the intervention effect pre-specified	Low risk	Point analysis is the point of intervention
Intervention unlikely to affect data collection	Low risk	Sources and methods were the same before and after the intervention
Incomplete outcome data (attrition bias) All outcomes	Low risk	No outcome data are missing
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes are objective
Selective reporting (reporting bias)	Low risk	All relevant outcomes in the Methods section are reported in the Results section
Other bias	Low risk	No other important bias is detected in the study

Yin 2008

Methods	CRMS, but treated as an RMS
Participants	Part D–eligible persons (n = 117 648)/Part D–ineligible persons (n = 59 663)
Interventions	Cap + Co-insurance + Ceiling (Medicare part D)
Outcomes	Medicine use; cost
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not applicable (treated as RMS)
Allocation concealment (selection bias)	Unclear risk	Not applicable (treated as RMS)

Yin 2008 *(Continued)*

Baseline outcome measurement similarity	Unclear risk	Not applicable (treated as RMS)
Baseline characteristics similarity	Unclear risk	Not applicable (treated as RMS)
Protection against contamination	Unclear risk	Not applicable (treated as RMS)
Intervention independent of other changes	Low risk	Intervention is independent of other relevant changes
Shape of the intervention effect pre-specified	Low risk	Point analysis is the point of intervention
Intervention unlikely to affect data collection	Low risk	Sources and methods were the same before and after the intervention
Incomplete outcome data (attrition bias) All outcomes	Low risk	Their approach assumes that absence of a prescription claim for an individual represents no utilisation for that person, rather than missing data
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Objective measures
Selective reporting (reporting bias)	Low risk	All relevant outcomes in the Methods section are reported in the Results section
Other bias	Low risk	No other important bias is detected in the study

Zhang 2009b

Methods	CRMS, but treated as RMS
Participants	USA Pennsylvania, Medicare part D
Interventions	Cap + Co-insurance + Ceiling (Medicare part D)
Outcomes	Cost
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not applicable (treated as RMS)
Allocation concealment (selection bias)	Unclear risk	Not applicable (treated as RMS)
Baseline outcome measurement similarity	Unclear risk	Not applicable (treated as RMS)

Zhang 2009b *(Continued)*

Baseline characteristics similarity	Unclear risk	Not applicable (treated as RMS)
Protection against contamination	Unclear risk	Not applicable (treated as RMS)
Intervention independent of other changes	Low risk	Intervention is independent of other relevant changes
Shape of the intervention effect pre-specified	Low risk	Point analysis is the point of intervention
Intervention unlikely to affect data collection	Low risk	Sources and methods were the same before and after the intervention
Incomplete outcome data (attrition bias) All outcomes	Low risk	No outcome data are missing
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes are objective
Selective reporting (reporting bias)	Low risk	All relevant outcomes in the Methods section are reported in the Results section
Other bias	Low risk	No other important bias is detected in the study

CBA: controlled before-after.
CRMS: Controlled Repeated Measure Studies.
DCF: data collection formulary.
FFS: fee-for-service.
HCFA: Health Care Financing Administration.
ITS: interrupted time series.
PBM: pharmacy benefits manager.
PBS: Pharmaceutical Benefits Scheme.
RAMQ: Régie de l'assurance maladie du Québec
RCT: randomised controlled trial.
RMS: repeated measures studies.

Characteristics of excluded studies [author-defined order]

Study	Reason for exclusion
Anis2005	Study uses an RMS design, but no specific intervention change is addressed
Balkrishnan2001	Study design - CBA with only 1 intervention and only 1 control site
Basu2008	CBA with only 1 intervention and 1 control site
Bazalo2012	No intervention change is addressed
Bishop 2009	Intervention is not met. All participants are followed for a total of 12 months. Nevertheless it is not clear if 3-point measures were assured before and after the intervention (variable period, according to the individual), as the turning point (point of analysis) is achievement of the cap

Study	Reason for exclusion
Bloom2003	CITS, but without 3 measures before and 3 after
Brian1974	Included in the first version of this systematic review. As criteria for CBA have been changed by Cochrane, this study is now excluded because it does not include 2 interventions and 2 control sites
Chang2005	Participants do not meet criteria. Intervention is applied in a limited setting
Colby2011	No intervention change is addressed
Cox2001	It is not clear how study authors controlled the exposition to characterise this as a NRCT. This is a survey based on a self administered questionnaire, not on reports before and after the intervention
Crane2010	No intervention change is addressed
Crown2004	Although it uses data from 1995-2000 and has a longitudinal design, this study does not provide data from before, only after, and the exposition is not controlled by the study author; no baseline data are provided. Investigators analyse the data only by type of co-payment and its relation (or not) to outcomes; they do not analyse data throughout time and do not provide data gathered before any intervention
Dhippayom2008	Study works with aggregate yearly measurements, not with analysis per month, and does not fit the criteria of at least 2 intervention and 2 control sites
Donohue2010	Study design does not meet criteria. 3 intervention groups and only 1 comparison group are included
Donohue2012	Type of study does not meet criteria - CBA with 3 intervention clusters but only 1 control cluster
Farley2010b	Study is a CITS but does not provide 3 points before and 3 after. Uses data from the Medical Expenditure Panel Survey (MEPS), applied each 4 to 5 months. Study uses 2005 and 2006 data (p 945)
Farley2010c	Study addresses the influence of Medicare part D implementation on the Medicaid programme; however, the Medicaid programme did not change throughout the years studied, which does not meet our inclusion criteria
Fu2010	Study is a CITS but does not include 3 points before and 3 after. Uses data from the Medical Expenditure Panel Survey (MEPS), applied each 4 to 5 months. Study uses 2005 and 2006 data (p 945)
Fung 2010	Study as designed does not assess the policy change at 1 specific point in time. Each enrollee achieves the gap at a different point of time. In the analysis, each enrollee is addressed 6 months before and 6 months after achieving the gap
Gibson 2005	CITS with only 1 control and 1 intervention site
Gibson2012	No intervention change
Goedken2009	Longitudinal study with few points of measurement
Goisis2002	Although this is an ITS, the intervention occurs over a long time, and 3 points before and 3 points after are not provided. "The processed data refers to the four-year period from 1997 to 2000 (when the cost-sharing amount decreased significantly) and includes an update of the first months of 2001, when the sensational effects of the increased expenditure could be seen as a result of the abolition of cost-sharing for the majority of drugs and for some healthcare services"
Gu2010b	No intervention change is addressed

Study	Reason for exclusion
Harris1990	Included in the first version of this systematic review. As criteria for CBA have been changed by Cochrane, this trial is now excluded because it does not include 2 interventions and 2 control sites
Holloway2001	This study is a CBA but includes only 1 control cluster; therefore it does not fit CBA criteria (Table 1)
Holmes2012	No intervention change
Huskamp2005	Included in the first version of this systematic review. As criteria for CBA have been changed by Cochrane, this study is now excluded because it does not include 2 interventions and 2 control sites
Johnston2012	Type of intervention does not meet criteria; no intervention change is included. Study analyses the relationship between combination antiretroviral therapy (cART) prescription cost sharing and adherence to initial cART
Kephart 2007	To be excluded, as results on ITS analysis are not presented in the paper. Results presented do not fit our inclusion criteria
Ketcham2008b	Study does not include 3 points before and 3 points after the policy change (2006). This is a case-control study
Kim2011c	No clear information is provided about the intervention, and study includes a small number of studied people (178 intervention and 202 control)
Klepser2007	Study is a CBA with only 1 intervention and 1 control site
Kozyrskyj2001	Included in the first version of this systematic review. As criteria for CBA have been changed by Cochrane, this study is now excluded because it does not include 2 interventions and 2 control sites
Landsman2005	This study is a CBA with only 1 intervention and 1 control site
Li2012a	Study as designed does not assess the policy change at 1 specific point in time. Each enrollee achieves the gap at a different point in time
Lingle1987	Included in the first version of this systematic review. As criteria for CBA have been changed by Cochrane, this study is now excluded because it includes only 1 intervention and 1 control site
Liu2003	Only 1 time point before and 1 time point after the intervention. Cross-sectional regression analysis and control group are not comparable. Non-cost-sharing group was much smaller than cost-sharing group in terms of the number of prescriptions
Maciejewski2010	Study uses a pre/post quasi-experimental design; however it includes only 1 control and 1 intervention site
Maciejewski2010b	Although the study uses 4 different medical centres, results are presented as an aggregate of 1 intervention group and 1 control group. Generalisability of the results is somewhat limited because the sample was drawn from 4 large Veterans Affairs Medical Centers (VAMCs). The reason these 4 were chosen is geographical dispersion
Marshall2007	Type of intervention does not meet criteria: no intervention change
Motheral1999	Included in the first version of this systematic review. As criteria for CBA have been changed by Cochrane, this study is now excluded because it includes only 1 intervention and 1 control site
Motheral2001	RM and CBA studies were applied in the original publication, but the study does not assess policy change at 1 specific point in time. Each enrollee achieves the gap at a different point in time. For CBA (see Table 3, page 1298), only 1 control and 1 intervention group are included

Study	Reason for exclusion
Mott2010	Study is a CBA with only 1 intervention and 1 control site
Nair2003	Study is a CBA, although it includes 2 control sites and only 1 intervention site
Nair2011a	No intervention change
NCT00566774	Intervention targeted is full drug coverage with intention to evaluate its impact on health outcomes. Additionally, study is aimed at only 1 specific health condition
O'Brien1989	Intervention is not met; no intervention change
O'Reilly2009	Intervention change points are not clearly defined
Palmer2011	No intervention change
Pettersson2012	Intervention does not meet criteria. No target intervention changes. Paper addresses changes in inclusion, exclusion or maintenance procedures for lipid-lowering drugs on the reimbursement list of Sweden
Pettersson2012b	No intervention change
Phillips2002	No defined intervention
Puig-Junoy2011	Study is a CBA with only 1 intervention and 1 control site
Raebel2008	Study is a CBA but does not include 2 interventions and 2 control clusters
Rector2003	Type of study does not meet criteria because no time points are included in the preintervention period; intervention occurs at the end of 1997, and the study uses data from 1998 and 1999 (period that also includes policy implementation)
Sawyer1983	Type of study is not clear. Graph that contains monthly measures is provided (Figure 1), but the analysis does not provide monthly data, and the periods are aggregated before and after; nevertheless, no control group is included
Schneeweiss 2007b	Not an ITS study. Trends are analysed in relation to one another, not separately. Prospective cohort study that does not meet our inclusion criteria
Schneeweiss2004	Intervention is a reimbursement list, the object of another Cochrane systematic review. Intervention is stopped, covering the cost of nebulised bronchodilators, steroids and cromoglycate, then the policy includes a formulary restriction for nebulised respiratory drugs in British Columbia
Schneeweiss2007c	Although each cohort had 15 measurement points (6 before; 9 after intervention), follow-up period was different for each cohort (consecutive cohort). Study authors state that adherence to statins is known as bad, independently from any intervention, including full coverage. Results show only a discrete effect, although it was statistically significant
Stroupe2007	CBA without 2 controls and 2 intervention sites
Subramanian2011	Study is a CBA with only 1 intervention group and 2 control groups
Sun2007	CBA with only 1 intervention group and only 1 control group. Fatally flawed
Taira2006	No intervention in the study. Investigators try to correlate co-payment levels with compliance rates
Tseng2004	Only 1 intervention group and 1 control group

Study	Reason for exclusion
Walberg2008	No intervention change. Study was conducted to estimate annual patient out-of-pocket costs in the stand-alone prescription drug plan (PDP) between 2007 and 2008 after implementation of Medicare part D
West2006	Only a specific medicine is addressed
White2009	Type of intervention does not meet criteria. Although Medicare part D is a target intervention, the aspect addressed is the list for coverage
Yang2007	Does not meet our type of study inclusion criteria
Ye2007a	No intervention change; study analyses relationships between different co-pay groups and adherence. Investigators run models to identify the presence of a relationship using different co-payment levels. No intervention policy
Zeber2007	Study design is unclear. If considered an ITS, only 2 points before and 2 points after intervention. If considered a CBA, only 1 control group
Zhang2009d	Medicare is a policy intervention, but no intervention change is made in the 12-month study period
Zhang2011	Study design does not meet minimum requirements, as study could be characterised as a CBA but does not meet the requirement of 2 control clusters. Data are measured early, with 2 measures before and 2 measures after the intervention
Zivin2009	Only 1 intervention and 1 control group. High risk of bias. Study is based on surveys

cART: combination antiretroviral therapy.
CBA: controlled before-after.
CITS: controlled interrupted time series.
MEPS: Medical Expenditure Panel Survey.
NRCT: Non-randomised controlled trials.
PDP: prescription drug plan.
RM: repeated measures.
RMS: repeated measures studies.
VAMCs: Veterans Affairs Medical Centers.

Characteristics of studies awaiting assessment *[ordered by study ID]*

Abraham2009

Methods	
Participants	
Interventions	
Outcomes	
Notes	Not possible to recover the complete paper

Almarsdottir2000

Methods	

Almarsdottir2000 *(Continued)*

Participants	
Interventions	
Outcomes	
Notes	Not possible to recover the complete paper

Banahan2011

Methods	
Participants	
Interventions	
Outcomes	
Notes	Not possible to recover the complete paper

Bennett1989

Methods	
Participants	
Interventions	
Outcomes	
Notes	Not possible to recover the complete paper

Byrne1990

Methods	
Participants	
Interventions	
Outcomes	
Notes	Not possible to recover the complete paper

Cifaldi2003

Methods	

Cifaldi2003 *(Continued)*

Participants	
Interventions	
Outcomes	
Notes	Not possible to recover the complete paper

Collins1996

Methods	
Participants	
Interventions	
Outcomes	
Notes	This study had considerable missing data. These data still need to be retrieved from the study authors.

Cubanski2004

Methods	
Participants	
Interventions	
Outcomes	
Notes	Not possible to recover the complete paper

D'Souza2010

Methods	
Participants	
Interventions	
Outcomes	
Notes	This study had considerable missing data. These data still need to be retrieved from the study authors.

Damiani2012

Methods	
Participants	
Interventions	
Outcomes	
Notes	This study had considerable missing data. These data still need to be retrieved from the study authors.

Doshi2009

Methods	
Participants	
Interventions	
Outcomes	
Notes	This study had considerable missing data. These data still need to be retrieved from the study authors.

Farley2010

Methods	
Participants	
Interventions	
Outcomes	
Notes	Not possible to recover the complete paper

Fryatt 1994

Methods	
Participants	
Interventions	
Outcomes	
Notes	This study had considerable missing data. These data still need to be retrieved from the study authors.

Gorsh2011

Methods	
Participants	
Interventions	
Outcomes	
Notes	Not possible to recover the complete paper

Hsu2009

Methods	
Participants	
Interventions	
Outcomes	
Notes	Not possible to recover the complete paper

Jonasson 2009

Methods	
Participants	
Interventions	
Outcomes	
Notes	Not possible to recover the complete paper

Joyce2009

Methods	
Participants	
Interventions	
Outcomes	
Notes	This study had considerable missing data. These data still need to be retrieved from the study authors.

Khanna2011

Methods	
Participants	
Interventions	
Outcomes	
Notes	Not possible to recover the complete paper

Kim2009b

Methods	
Participants	
Interventions	
Outcomes	
Notes	Not possible to recover the complete paper

Kimmel2009

Methods	
Participants	
Interventions	
Outcomes	
Notes	Not possible to recover the complete paper

Landon2007

Methods	
Participants	
Interventions	
Outcomes	
Notes	This study had considerable missing data. These data still need to be retrieved from the study authors.

Lee2006

Methods	
Participants	
Interventions	
Outcomes	
Notes	This study had considerable missing data. These data still need to be retrieved from the study authors.

Lee2011

Methods	
Participants	
Interventions	
Outcomes	
Notes	This study had considerable missing data. These data still need to be retrieved from the study authors.

Liu2004

Methods	
Participants	
Interventions	
Outcomes	
Notes	This study had considerable missing data. These data still need to be retrieved from the study authors.

Liu2011

Methods	
Participants	
Interventions	
Outcomes	
Notes	This study had considerable missing data. These data still need to be retrieved from the study authors.

Lo Sasso2006

Methods	
Participants	
Interventions	
Outcomes	
Notes	This study had considerable missing data. These data still need to be retrieved from the study authors.

Maciejewski2010d

Methods	
Participants	
Interventions	
Outcomes	
Notes	Not possible to recover the complete paper

Mahabaleshwarkar2011

Methods	
Participants	
Interventions	
Outcomes	
Notes	Not possible to recover the complete paper

Martin 1996

Methods	
Participants	
Interventions	
Outcomes	
Notes	This study had considerable missing data. These data still need to be retrieved from the study authors.

Morgan2006c

Methods	
Participants	
Interventions	
Outcomes	
Notes	This study had considerable missing data. These data still need to be retrieved from the study authors.

Reiss2011

Methods	
Participants	
Interventions	
Outcomes	
Notes	This study had considerable missing data. These data still need to be retrieved from the study authors.

Rodin2009

Methods	
Participants	
Interventions	
Outcomes	
Notes	This study had considerable missing data. These data still need to be retrieved from the study authors.

Setoguchi2009

Methods	
Participants	
Interventions	
Outcomes	
Notes	Not possible to recover the complete paper

Teixeira 2010

Methods	
Participants	
Interventions	
Outcomes	
Notes	Not possible to recover the complete paper

Teixeira2010

Methods	
Participants	
Interventions	
Outcomes	
Notes	This study had considerable missing data. These data still need to be retrieved from the study authors.

Thengilsdttir2010

Methods	
Participants	
Interventions	
Outcomes	
Notes	Not possible to recover the complete paper

Thompson2011

Methods	
Participants	
Interventions	
Outcomes	
Notes	Not possible to recover the complete paper

Wang2010b

Methods	
Participants	
Interventions	
Outcomes	
Notes	This study had considerable missing data. These data still need to be retrieved from the study authors.

Wang2011b

Methods	
Participants	
Interventions	
Outcomes	
Notes	Not possible to recover the complete paper

Winkelmann2004

Methods	
Participants	
Interventions	
Outcomes	
Notes	This study had considerable missing data. These data still need to be retrieved from the study authors.

Zeber2011

Methods	
Participants	
Interventions	
Outcomes	
Notes	Not possible to recover the complete paper

Zhang2010	
Methods	
Participants	
Interventions	
Outcomes	
Notes	This study had considerable missing data. These data still need to be retrieved from the study authors.

Zhang2010a	
Methods	
Participants	
Interventions	
Outcomes	
Notes	This study had considerable missing data. These data still need to be retrieved from the study authors.

ADDITIONAL TABLES

Table 1. Factors that could modify the effects of co-payments or cap policies

FACTOR	CONDITION	POTENTIAL EFFECTS
Size of cap/co-payment	Effect of the policy will be dependent on how strict the co-payment policy is (i.e. size of co-payment, time and volume included in cap or ceiling, period of time included in maximum co-payment policies, etc)	**If too strict:** *Medicine use:* decrease *Health*: decrease *Healthcare utilisation:* increase *Patient medicine expenditures:* increase *Insurer medicine expenditures:* decrease *Other insurer expenditures:* increase **If too generous:** *Medicine use:* no change/increase *Health*: no change *Healthcare utilisation:* no change *Patient medicine expenditures:* no change

Table 1. Factors that could modify the effects of co-payments or cap policies *(Continued)*

		Insurer medicine expenditures: no change/increase *Other insurer expenditures:* no change
Medicine groups	Suitable medicine groups should be included in the policy. Most co-payment policies aim to reduce overuse of medicines and to control expenditures, targeting particularly "less-essential" medicines. However, when co-payments are applied to all prescription medicines in general, risk of discontinuation of important medicines occurs Also, consuming behaviour from patient perspective will be affected by his perception of need. Patients may be more motivated to not interrupt symptomatic treatment than asymptomatic treatment. This premise is based on the assumption that patients will be more likely to use medicines in symptomatic situations. In relation to asymptomatic situations, patients are likely to not use medicines because of changes in expenditures or health illiteracy (Ref Leibowitz 1989)	**Symptomatic treatment medicines** *Medicine use*: no change *Health*: no change *Healthcare utilisation*: no change *Patient medicine expenditures*: increase *Insurer medicine expenditures*: decrease *Other insurer expenditures:* no change **Asymptomatic treatment medicines** *Medicine use*: decrease *Health*: decrease/no change *Healthcare utilisation*: increase/no change *Patient medicine expenditures*: no change/decrease *Insurer medicine expenditures*: decrease *Other insurer expenditures:* increase
Vulnerable populations	Ensuring that all patients have access to, and can afford, important life-sustaining medicines. Low-income, elderly and disabled people are especially sensitive towards co-payments, and increased medicine expenses may cause discontinuation of important medicines. Not taking this population into consideration, the policy may result in higher healthcare utilisation, deterioration of health and higher overall healthcare expenditures When experiencing chronic conditions, these vulnerable groups that are in need of multiple medicines may be particularly susceptible to co-payment policies as they are more likely to exceed any cap levels, or to use a large number of medicines that may add up to large co-payments	*Medicine use*: decrease *Health*: decrease *Healthcare utilisation:* increase *Patient medicine expenditures:* increase *Insurer medicine expenditures:* decrease *Other insurer expenditures:* increase
Enforcement	Adequate incentives for enforcer to comply with the policy. Co-payments in most cases are enforced by pharmacists or by the physician	*Medicine use:* no change *Health:* no change *Healthcare utilisation:* no change *Patient medicine expenditures:* no change/increase *Insurer medicine expenditures:* decrease/no change *Other insurer expenditures:* no change
Patient level of information	Adequate follow-up and information provided to patients. As many co-payment policies expect patients to prioritise use of important and life-sustaining medicines over "less essential medicines", much responsibility is put on patients to make good choices about their own health and knowledge of pharmacotherapy. However,	*Medicine use:* no change (in important medicines) *Health:* increase *Healthcare utilisation:* no change *Patient medicine expenditures:* no change/decrease

Table 1. Factors that could modify the effects of co-payments or cap policies *(Continued)*

	without enough information, patients may choose differently, for example, prioritising "less essential" medicines that are associated with more rapidly experienced discomfort if discontinued	*Insurer medicine expenditures:* no change *Other insurer expenditures:* no change/decrease
Enforcer level of information	Adequate follow-up and information provided to enforcer. How much information prescribers or pharmacists have about the policy concerning prescription and dispensation of medicines and how involved the patient is in the decision making are important factors Also, to what extent the enforcer is informed about the price of medicines, medicine substitution possibilities or patients' ability to pay may influence the impact of the policy Potential consequences may be that use of medicines is unchanged, and that further economic strain is put on the patient (instead of, for example, substituting for less expensive medicines)	*Medicine use:* no change/increase *Health*: no change *Healthcare utilisation:* no change *Patient medicine expenditures:* no change/decrease *Insurer medicine expenditures*: decrease *Other insurer expenditures:* no change
Exemptions	Reasonable mechanisms for patients who need exemptions for medical reasons. However, too generous exemptions may minimise potential effects of the policy In some cases, the pharmacist or the physician has the power to exempt patients from co-payments, but then will be liable for these expenses themselves. If such an exemption is easily attainable for the patient, little reduction in medicine use can be expected, although the policy may still save third-party expenditures. Instead of a shift of cost from insurer to patient, a shift of cost occurs from insurer to enforcer [VL1]	**If too strict:** *Medicine use:* decrease *Health:* decrease *Healthcare utilisation:* increase *Patient medicine expenditures:* increase *Insurer medicine expenditures:* decrease *Other insurer expenditures:* increase **If too generous:** *Medicine use:* no change/increase *Health:* no change *Healthcare utilisation:* no change *Patient medicine expenditures:* no change/decrease *Insurer medicine expenditures:* no change/increase *Other insurer expenditures:* no change **Reasonable:** *Medicine use:* no change *Health:* no change *Healthcare utilisation:* no change *Patient medicine expenditures:* no change *Insurer medicine expenditures:* no change *Other insurer expenditures:* no change

Table 2. GRADE: Cap

Questions	Should cap be used for rational use of medicines?
Comparison	Cap versus broader or no restriction on time of refills and number of prescriptions
Participant characteristics	Vulnerable and general populations
Setting	USA and Australia
Target population (of the policy)	Low-income (Medicaid) and general populations (PBS-Australia)

Number of studies	**Design**	**Risk of bias**	**Inconsistency (i)**	**Indirectness (ii)**	**Imprecision**	**Other**	**Quality (overall score)**
Outcome: use of medicines – overall							
3 (2 ITS[1], 1 RMS[2])	(2)	Not serious (0)	Not serious (0)	Not serious (0)	Not serious (0)	Not serious	Low (2)
Outcome: use of medicines – medicines for symptomatic conditions							
3 (1 ITS[3]; 2 RMS[4])	(2)	Not serious (0)	Not serious (0)	Not serious (0)	Not serious (0)	Not serious	Low (2)
Outcome: use of medicines – medicines for asymptomatic conditions							
0	–	–	–	–	–	–	–
Outcome: cost – patient perspective							
0	–	–	–	–	–	–	–
Outcome: cost – insurer perspective (expenditures on medicines)							
3 (1 ITS[3]; 2 RMS[4])	(2)	Not serious (0)	Not serious (0)	Not serious (0)	Not serious (0)	Not serious (0)	Low (2)
Outcome: cost – insurer perspective (on health care)							
0	–	–	–	–	–	–	–

Table 2. GRADE: Cap *(Continued)*

Outcome: healthcare utilisation – overall healthcare utilisation							
0	–	–	–	–	–	–	–
Outcome: healthcare utilisation – emergency department and hospitalisation							
2 (1 ITS[3]; 1 RMS[5])	(2)	Not serious (0)	Not serious (0)	Not serious (0)	Serious (-1)	Not serious (0)	Very low (1)
Outcome: healthcare utilisation – outpatient care							
1 RMS[5]	(2)	Not serious (0)	Not serious (0)	Not serious (0)	Not serious (0)	Serious (-1)	Very low (1)
Outcome: health outcome							
0	–	–	–	–	–	–	–

1. Soumerai 1991; Donnelly 2000.
2. Soumerai 1987.
3. Cromwell 1999.
4. Soumerai 1987; Soumerai 1994.
5. Soumerai 1994.

Table 3. GRADE: Cap + Co-insurance + Ceiling

Questions	Should Cap combined with Ceiling and Co-insurance be used for rational use of medicines?
Comparison	Caps combined with Ceiling and Co-insurance versus heterogeneous but limited medicines coverage
Participant characteristics	Vulnerable population: senior, 65 years of age or older
Setting	USA
Target population (of the policy)	Seniors

Number of studies	Design	Risk of bias	Inconsistency (i)	Indirectness (ii)	Imprecision	Other	Quality (overall score)

Table 3. GRADE: Cap + Co-insurance + Ceiling *(Continued)*

Outcome: use of medicines – overall							
1 RMS[1]	(2)	Not serious (0)	Not serious (0)	Not serious (0)	Not serious (0)	Not serious (0)	Low
Outcome: use of medicines – medicines for symptomatic conditions							
4 (2 ITS[2]; 2 RMS[3])	(2)	Not serious (0)	Not serious (0)	Not serious (0)	Not serious (0)	Not serious (0)	Low
Outcome: use of medicines – medicines for asymptomatic conditions							
2 (ITS[4]; RMS[5])	(2)	Not serious (0)	Not serious (0)	Not serious (0)	Not serious (0)	Not serious (0)	Low
Outcome: cost – patient perspective							
5 (2 ITS[6]; 3 RMS[7])	(2)	Not serious (0)	Not serious (0)	Not serious (0)	Not serious (0)	Not serious (0)	Low
Outcome: Cost – insurer perspective (expenditures on medicines)							
0	–	–	–	–	–	–	-
Outcome: cost – insurer perspective (on health care)							
0	–	–	–	–	–	–	–
Outcome: healthcare utilisation – overall healthcare utilisation							
0	–	–	–	–	–	–	–
Outcome: healthcare utilisation – emergency department and hospitalisation							
0	–	–	–	–	–	–	–
Outcome: healthcare utilisation – overall healthcare utilisation							
0	–	–	–	–	–	–	–
Outcome: drug use – outpatient care							
0	–	–	–	–	–	–	–
Outcome: health outcome							

Table 3. GRADE: Cap + Co-insurance + Ceiling *(Continued)*

0	–	–	–	–	–	–	–

1. Yin 2008.
2. Chen 2008b; Shrank 2008.
3. Schneeweiss 2009; Polinski 2012.
4. Shrank 2008.
5. Schneeweiss 2009.
6. Shrank 2008; Polinski 2012.
7. Yin 2008; Schneeweiss 2009; Zhang 2009b.

Table 4. GRADE: Fixed co-payment

Questions	Does the increase in fixed co-payment affect rational use of medicines?
Comparison	Lower value of fixed co-payment or full drug coverage
Participant characteristics:	Elderly/General populations
Setting	High-income countries (US, CN, Sweden)
Target population (of the policy)	Seniors and general population

Number of studies	**Design**	**Risk of bias**	**Inconsistency (i)**	**Indirectness (ii)**	**Imprecision**	**Other**	**Quality (overall score)**
Outcome: use of medicines – overall							
2 ITS[1]	(2)	Serious (-1)	Not serious (0)	Not serious (0)	Not assessed (0)	Not serious (0)	Very low
Outcome: use of medicines – medicines for symptomatic conditions							
3 ITS[2]	(2)	Not serious (0)	Not serious (0)	Not serious (0)	Not assessed (0)	Not serious (0)	Low
Outcome: use of medicines – medicines for asymptomatic conditions							
3 ITS[3]	(2)	Not serious (0)	Not serious (0)	Not serious (0)	Not assessed (0)	Not serious (0)	Low
Outcome: cost – patient perspective							

Table 4. GRADE: Fixed co-payment *(Continued)*

0	–	–	–	–	–	–	–
Outcome: cost – insurer perspective (expenditures on medicines)							
3 ITS[4]	2	Not serious (0)	Not serious (0)	Not serious (0)	Not serious (0)	Not serious (0)	Low
Outcome: cost – insurer perspective (on health care)							
0	–	–	–	–	–	–	–
Outcome: healthcare utilisation – overall healthcare utilisation							
0	–	–	–	–	–	–	–
Outcome: healthcare utilisation – emergency department and hospitalisation							
0	–	–	–	–	–	–	–
Outcome: healthcare utilisation – outpatient care							
0	–	–	–	–	–	–	–
Outcome: health outcome							
0	–	–	–	–	–	–	–

1. Nelson 1984; Hux 1997.
2. Hux 1997; Ong 2003;Reeder 1985.
3. Reeder 1985; Hux 1997; Roblin 2005.
4. Sawyer 1982; Nelson 1984; Hux 1997.

Table 5. GRADE: Tier + Fixed co-payment

Questions	Should the implementation of/increase in tier combined with fixed co-payment be used for rational use of medicines?
Comparison	Full medicine coverage/2-tier
Participant characteristics	Vulnerable population (retirees and low-income)
Setting	USA

Table 5. GRADE: Tier + Fixed co-payment *(Continued)*

Target population (of the policy)	Employees; vulnerable population

Number of studies	Design	Risk of bias	Inconsistency (i)	Indirectness (ii)	Imprecision	Other	Quality (overall score)
Outcome: use of medicines – overall							
2 (ITS[1]; CBA[2])	(2)	Not serious (0)	Serious (-1)	Not serious (0)	Not serious (0)	Dose-response effect (1)	Low
Outcome: use of medicines – medicines for symptomatic conditions							
1 CBA[2]	(2)	Not serious (0)	Not serious (0)	Not serious (0)	Not serious (0)	Not serious (0)	Low
Outcome: use of medicines – medicines for asymptomatic conditions							
1 CBA[2]	(2)	Not serious (0)	Not serious (0)	Not serious (0)	Not serious (0)	Not serious (0)	Low
Outcome: cost – patient perspective							
0	–	–	–	–	–	–	–
Outcome: cost – insurer perspective (expenditures on medicines)							
0	–	–	–	–	–	–	–
Outcome: cost – insurer perspective (on health care)							
0	–	–	–	–	–	–	–
Outcome: healthcare utilisation – overall healthcare utilisation							
0	–	–	–	–	–	–	–
Outcome: healthcare utilisation – emergency department and hospitalisation							
1 ITS[1]	(2)	Not serious (0)	Not serious (0)	Not serious (0)	Serious (-1)	Not serious (0)	Very low
Outcome: healthcare utilisation – outpatient care							

Table 5. GRADE: Tier + Fixed co-payment *(Continued)*

1 ITS[1]	(2)	Not serious (0)	Not serious (0)	Not serious (0)	Serious (-1)	Not serious (0)	Very low
Outcome: health outcome							
0	–	–	–	–	–	–	–

1. Hartung 2008.
2. Huskamp 2007.

Table 6. GRADE: Ceiling + Fixed co-payment

Questions	Should implementation of or increase in ceiling combined with fixed co-payment be used for rational use of medicines?
Comparison	Full medicines coverage, lower fixed co-payment and ceiling amounts
Participant characteristics	Low-income/General populations
Setting	High-income countries (Australia, Canada and Sweden)
Target population (of the policy)	General population

Number of studies	Design	Risk of bias	Inconsistency (i)	Indirectness (ii)	Imprecision	Other	Quality (overall score)
Outcome: use of medicines – overall							
5 (4 ITS[1], 1 CBA[2])	(2)	Not serious (0)	Not serious (0)	Not serious (0)	Not assessed (0)	Not serious (0)	Low
Outcome: use of medicines – medicines for symptomatic conditions							
6 (1RMS[3]; 4 ITS[4]; 1 CBA[2])	(2)	Not serious (0)	Not serious (0)	Not serious (0)	Not serious (0)	Not serious (0)	Low
Outcome: use of medicines – medicines for asymptomatic conditions							
4 (3 ITS[5]; 1 CBA[2])	(2)	Not serious (0)	Not serious (0)	Not serious (0)	Not assessed (0)	Not serious (0)	Low
Outcome: cost – patient perspective							

Table 6. GRADE: Ceiling + Fixed co-payment *(Continued)*

0	–	–	–	–	–	–	–
Outcome: cost – insurer perspective (expenditures on medicines)							
2 (ITS[6])	(2)	Serious (-1)	Not serious (0)	Not serious (0)	Not serious (0)	Not serious (0)	Very low
Outcome: cost – insurer perspective (on health care)							
0	–	–	–	–	–	–	–
Outcome: healthcare utilisation – overall healthcare utilisation							
0	–	–	–	–	–	–	–
Outcome: healthcare utilisation – emergency department and hospitalisation							
1 RMS[7]	(2)	Not serious (0)	Not serious (0)	Not serious (0)	Not serious (0)	Not serious (0)	Low
Outcome: healthcare utilisation – outpatient care							
1 RMS[7]	(2)	Not serious (0)	Not serious (0)	Not serious (0)	Not serious (0)	Not serious (0)	Low
Outcome: ***Health outcome***							
0	–	–	–	–	–	–	–

1. Andersson 2006; McManus 1996; Hynd 2008; Hynd 2009.
2. Poirier 1998.
3. Dormuth 2006.
4. McManus 1996; Hynd 2008; Wang 2008b; Hynd 2009.
5. Caetano 2006; Hynd 2008; Hynd 2009.
6. Andersson 2006; Dormuth 2009.
7. Dormuth 2008.

Table 7. GRADE: Ceiling + Co-insurance

Questions	Should restrictive ceiling combined with co-insurance be used for rational use of medicines?
Comparison	Full medicines coverage, fixed co-payment and lower co-insurance
Participant characteristics	General population

Table 7. GRADE: Ceiling + Co-insurance *(Continued)*

Setting	Canada, EUA and Sweden
Target population (of the policy)	General and vulnerable populations

Number of studies	Design	Risk of bias	Inconsistency (i)	Indirectness (ii)	Imprecision	Other	Quality (overall score)
Outcome: use of medicines – overall							
3 (RCT[1], ITS[2], RMS[3])	(3)	Serious (-1)	Not serious (0)	Not serious (0)	Not serious (0)	Dose response (1)	Moderate
Outcome: use of medicines – medicines for symptomatic conditions							
5 (RCT[1]; 3 ITS[4]; RMS[5])	(2)	Not serious (0)	Not serious (0)	Not serious (0)	Not serious (0)	Not serious (0)	Low
Outcome: use of medicines – medicines for asymptomatic conditions							
2 ITS[6]	(2)	Not serious (0)	Not serious (0)	Serious (-1)	Not serious (0)	Not serious (0)	Very low
Outcome: cost – patient perspective							
0	–	–	–	–	–	–	–
Outcome: cost – insurer perspective (expenditures on medicines)							
2 (RCT[1]; ITS[2])	(3)	Serious (-1)	Not serious (0)	Not serious (0)	Not serious (0)	Dose response (1)	Moderate
Outcome: cost – insurer perspective (on health care)							
0	–	–	–	–	–	–	–
Outcome: healthcare utilisation – overall healthcare utilisation							
0	–	–	–	–	–	–	–
Outcome: healthcare utilisation – emergency department and hospitalisation							

Table 7. GRADE: Ceiling + Co-insurance *(Continued)*

1 RMS[7]	(2)	Not serious (0)	Not serious (0)	Not serious (0)	Not serious (0)	Not serious (0)	Low
Outcome: healthcare utilisation – outpatient care							
1 RMS[7]	(2)	Not serious (0)	Not serious (0)	Not serious (0)	Serious (-1)	Not serious (0)	Very low
Outcome: health outcome							
0	–	–	–	–	–	–	–

1. Newhouse 1993.
2. Andersson 2006 (two interventions).
3. Tamblyn 2001 (two interventions).
4. Blais 2002; Ong 2003; Wang 2008b.
5. Dormuth 2006.
6. Blais 2002; Caetano 2006.
7. Dormuth 2008.

Table 8. Categories of medicines according to classification as symptomatic or asymptomatic

Symptomatic medicines	Asymptomatic medicines
Acetic acid derivates and related substances (M01AB), a group of non-steroidal anti-inflammatory medicines (NSAIDs) - non-steroidal anti-inflammatory medicines (NSAIDs))	Acetic acid derivates (as antiplatelets)
Analgesics/Antipyretics	Alpha-antagonists,
Antiepileptics	Amphetamines, stimulants
Antigout preparations	Angiotensin-converting enzyme (ACE) inhibitors
Anti-Parkinson's treatments	Angiotensin receptor blockers (ARBs)
Antibiotics - cephalosporins, macrolide antibiotics, penicillins	Antihyperlipidemic medicines
Anticholinergic inhalers with chronic obstructive pulmonary disease or asthma	Antihypertensives (e.g., reserpine)
Anticonvulsants	Beta-adrenergic agonists
Antidepressants	Calcium channel blockers (CCBs)
Antidepressants: selective serotonin-reuptake inhibitors, SSRIs (N06AB), a group of antidepressants - selective serotonin-reuptake inhibitors (SSRIs)	Contraceptives
Antihistamines	Glaucoma treatments
Antipsychotics - antipsychotics psychosis, antipsychotics	Non-aspirin antiplatelets (e.g. clopidogrel)
Antipsychotics psychosis	Non-thiazide diuretics
Antipsychotics	Oral antidiabetic agents
Anxiolytics/sedatives/hypnotics - "Benzodiazepines – benzodiazepines, clonazepam, medicines for depression"	Osteoporosis treatment
Benzodiazepines	Statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) blockers (ARBs), b-blockers,
Benzodiazepines	thiazide diuretics
Beta-2-agonists	Thyroxine
Beta-2-adrenoreceptor agonists, a group of bronchodilators (R03CA)	Beta-blockers
Cell stabilisers (eg, cromolyn),	
Clonazepam	
Corticosteroids	
Cough and cold products	
Medicines for depression	
Insulin	
Insulin (A10A)	
Macrolide antibiotics	
Muscle relaxants	
Non-steroidal anti-inflammatories	
Non-steroidal anti-inflammatory medicines (NSAIDs))	

Table 8. Categories of medicines according to classification as symptomatic or asymptomatic *(Continued)*

Opioid analgesics
Penicillins
Proton pump inhibitors
Salicylates
Selective serotonin-reuptake inhibitors, SSRIs (N06AB), a group of antidepressants
Adrenergics
Cholinergics
Gastrointestinals
Psychotherapeutics

Table 9. Abbreviations

AUD	Australian dollar
BC	British Columbia
ADHD	Attention deficit hyperactivity disorder
ARIMA	Autoregressive integrated moving average
CAD	Canandian dollar
CAE	Chronic obstructive pulmonary disease, asthma or emphysema
CBA	Control before-after
CI	Confidence interval
CITS	Controlled interrupted time series
CRM	Controlled repeated measures
DDD	Defined daily dose. A standardised concept established by the WHO. A DDD is the assumed average maintenance dose per day for a medicine used for its main indication in adults
ED	Emergency department
ER	Emergency room
FFS	Fee-for-service
ITS	Interrupted time series
MPR	Medication possession ratio
NSAID	Non-steroidal anti-inflammatory drug

Table 9. Abbreviations *(Continued)*

OECD	Organisation for Economic Co-operation and Development
PBS	Pharmaceutical Benefits Schemes (Australia)
PHMPM	Prescriptions dispensed per hundred members per month
PPI	Proton pump inhibitor
PUD	Peptic ulcer disease
RBP	Reference-based pricing
RCT	Randomised controlled trial
RM	Repeated measures
RR	Risk ratio (intervention vs control group)
RR (adj)	Risk ratio (adjusted for preintervention differences) = RR post intervention/RR preintervention
SEK	Swedish crowns
SS	Social security
SSRI	Selective serotonin-reuptake inhibitor
USA	United States of America
USD	USA dollars
WHO	World Health Organization

Table 10. Description of interventions: Cap

Rev ID	Intervention	Comparision	Population	Medicines addressed in the paper	Exemptions/modifiers	Intervention period
Cromwell 1999	1 antiulcer medicine prescribed with only 1 refill	No restrictions	Florida population, USA	Antiulcer	Coverage for high-dose prescription treatment for acute disorders was limited to 60 days	January 1989-August 1991 (quarterly data). Date of announcement August 1991, but study authors defined this as prepolicy. Date of implementation February 15 1992-December 1993 (quarterly data)
Donnelly 2000	20-Day minimum re-supply	3-Day minimum	Australia, whole	All prescription medicines	Pharmacists could override the re-supply rule	January 1991-June 2000

Table 10. Description of interventions: Cap *(Continued)*

	cap for medicines with 5 or more repeats, PBS items and eyedrops increased to 4 days	re-supply cap for all medicines	population			
Soumerai 1987	3 prescriptions per month and allowable quantity of per prescription tripled per patient reimbursed	No restrictions	Medicaid enrollees	Overall medicines **Essential** (insulin, propranolol, thiazides, furosemide, methyldopa, lithium, digoxin, anxiolytic and hypnotic agents, depressants and lithium, antipsychotics) **Symtomatic relief medicines** (analgesics, anti-inflammatory, aspirin, acetaminophen, propoxyphene (in combination with aspirin or acetaminophen), ibuprofen) **Limited efficacy medicines** (ergoloid mesylates, barbiturate-anticholinergic combination agent, donnatal propoxyphene without aspirin or acetaminophen, anticholinergic dicyclomine)	Programme for the first time restricted the number of prescriptions reimbursed to a maximum of 3 per patient per month; thus, with adequate communication among stat officials, patients and physicians, it was feasible to stagger prescriptions so that a patient could receive up to 9 drugs, thus reducing the effect of the legislation	September 1981-July 1982
Soumerai 1991	Same as Soumerai 1987 (same study)	Same as Soumerai 1987 (same study)	Same as Soumerai 1987 (same study)	Overall (medicines for which sudden withdraw was liable to precipitate institutionalisation and others commonly commonly used to treat chronic health problems)	Same as Soumerai 1987 (same study)	Same as Soumerai 1987 (same study)
Soumerai 1994	Same as Soumerai 1987 (same study)	Same as Soumerai 1987 (same study)	Same as Soumerai 1987 (same study)	Antipsychotic agents Anxiolytic and hypnotic agents Depressants and lithium	Same as Soumerai 1987 (same study)	Same as Soumerai 1987 (same study)

Table 11. Description of interventions: Cap + Co-insurance + Ceiling

Rev ID	Intervention	Comparision	Population	Medicines addressed	Exemptions/Modifiers	Intervention period

Table 11. Description of interventions: Cap + Co-insurance + Ceiling *(Continued)*

				in the paper		
Chen 2008b	Standard benefit for Medicare part D has a $32 monthly premium and a $250 deductible, then co-insurance of 25% up to $2250 in total medicines costs, followed by a gap in coverage between $2250 and $5100, where enrollees pay 100% of the costs of their medications. After enrollees have incurred $3600 in out-of-pocket expenses, they qualify for catastrophic coverage and pay 5% of medication costs	48% of beneficiaries had relatively generous medicines coverage through their former employer or Medicaid. One-third had more limited coverage through a privately purchased Medigap plan or a Medicare Advantage plan, and 18% had no coverage whatsoever	Medicare enrolles	Antidepressants Antipsychotics Benzodiazepines	After enrollees have incurred $3600 in out-of-pocket expenses, they qualify for catastrophic coverage and pay 5% of medication costs. Implementation of Medicare part D extensively expands the role of Medicare in financing mental health care. Most psychotropic prescriptions filled by seniors are now paid by Medicare. Beneficiaries with income below 100% of the federal poverty level pay a co-payment of $1 for each generic prescription and $3 for each brand name prescription. Those with income above 100% of the poverty level pay $2 and $5, respectively. In addition, the new medicines benefit includes substantial premium and cost-sharing subsidies (low-income subsidy) for Medicare beneficiaries with low income and modest resources	January 2005-December 2006
Polinski 2012	Standard benefit for Medicare part D for 2006 has a $32 monthly premium and a $250 deductible, then co-insurance of 25% up to $2250 in total medicines costs, followed by a gap in coverage between $2250 and $5100, where enrollees pay 100% of the costs of their medications. After enrollees have incurred $3600 in out-of-pocket expenses, they qualify for catastrophic coverage and pay 5% of medication costs	Not reported	Elderly patients	Antipsychotic medication	Not reported	January 2005-December 2006
Schneeweiss 2009	Standard benefit for Medicare part D for 2006 has a $32 monthly premium and a $250 deductible, then co-insurance of 25% up to $2250 in total medicines costs, followed by a gap in coverage between $2250 and $5100, where enrollees pay 100% of the costs of their medications. After enrollees have incurred $3600 in out-of-pocket expenses, they qualify for catastrophic cov-	No mediciness coverage, full price	Elderly patients enrolled in Medicare part D in 2006	Clopidogrel, warfarin, proton pump inhibitors (PPIs)) and statins	PBS items and eyedrops increased to 4 days	January 2005 –December 2006

Table 11. Description of interventions: Cap + Co-insurance + Ceiling *(Continued)*

	erage and pay 5% of medication costs					
Shrank 2008	Standard benefit for Medicare part D for 2006 has a $32 monthly premium and a $250 deductible, then co-insurance of 25% up to $2250 in total medicines costs, followed by a gap in coverage between $2250 and $5100, where enrollees pay 100% of the costs of their medications. After enrollees have incurred $3600 in out-of-pocket expenses, they qualify for catastrophic coverage and pay 5% of medication costs	Medicaid beneficieries	Elderly patients, dual eligibles, Medicare and Medicaid	Statins, proton pump inhibitors, warfarin, clopidogrel, benzodiazepines	Not reported	January 2005-December 2006
Yin 2008	Standard benefit for Medicare part D for 2006 has a $32 monthly premium and a $250 deductible, then co-insurance of 25% up to $2250 in total medicines costs, followed by a gap in coverage between $2250 and $5100, where enrollees pay 100% of the costs of their medications. After enrollees have incurred $3600 in out-of-pocket expenses, they qualify for catastrophic coverage and pay 5% of medication costs	Not reported	Medicare enrollees	Overall medicines	Not reported	September 1, 2004-April 31, 2007
Zhang 2009b	Standard benefit for Medicare part D for 2006 has a $32 monthly premium and a $250 deductible, then co-insurance of 25% up to $2250 in total medicines costs, followed by a gap in coverage between $2250 and $5100, where enrollees pay 100% of the costs of their medications. After enrollees have incurred $3600 in out-of-pocket expenses, they qualify for catastrophic coverage and pay 5% of medication costs	Not reported	Medicare part D enrollees in Pensylvania, USA	Overall medicines	”(...) beneficiaries faced a strong financial incentive to fill prescriptions in the insurer network: they received a 15% discount off-prices charged cash payers on average”	January 2004-December 2007

Table 12. Description of interventions: Cap + Fixed co-payment

Rev ID	Intervention	Comparision	Population	Medicines addressed in the paper	Exemptions/ Modifiers	Intervention period	Results
Andersson 2006 (3)	Structure of co-payment changed for per dispensing occasion: maximum SEK 125 for 1 prescription + SEK 25 per additional prescription and increased annual co-payment maximum (SEK 1700)	Annual co-pay max SEK 1600	Swedish population	Indicators groups: (1) Acetic acid derivates and related substances (M01AB), a group of non-steroidal anti-inflammatory medicines (NSAIDs). Medicines in the group: Acetic acid derivatives could also be affected by RBP, as patents had expired when RBP was introduced in 1993 (2) Selective serotonin-reuptake inhibitors, SSRIs (N06AB), a group of antidepressants	Not reported	January 1, 1993-December 31, 1996	
Ong 2003 (1)	160 initial fixed co-payments, after which patients pay 60 SEK for additional medicines	Co-payment per dispensing occasion: maximum SEK 125 for 1 prescription + SEK 25 per additional prescription and increased annual co-payment maximum (SEK 1700)	All outpatients from Stockholm, Sweden	Antidepressants Sedatives	Not reported	July 1994-July 1995	

Table 13. Description of interventions: Fixed co-payment

Rev ID	Intervention	Comparison	Population	Medicines addressed in the paper	Exemptions/Modifiers	Intervention period
Hux 1997	Low income: $2 fixed co-payment per prescription High income: $100 initial medicines co-payment, after which patients paid $6.11 per prescription	Full medicines coverage	All beneficiaries from the Ontario drug benefit programme	ACE inhibitors Beta-blockers Digoxin Furosemide L-thyroxine Oral hypoglycaemics Antipsychotics Sedatives NSAIDs Laxatives Muscle relaxants Lipid-lowering medicines	Not reported	January 1994–March 1997
Nelson 1984	Same as Reeder 1985 (same study)	Same as Reeder 1985 (same study)	Same as Reeder 1985 (same study)	Overall medicines	Same as Reeder 1985 (same study)	Same as Reeder 1985 (same study)
Ong 2003	160 initial fixed co-payments, after which patients pay 60 SEK for additional medicines	Co-payment per dispensing occasion: maximum SEK 125 for 1 prescription + SEK 25 per additional prescription and increased annual co-payment maximum (SEK 1700)	All outpatients from Stockholm, Sweden	Antidepressants Sedatives	Not reported	July 1994-July 1995
Reeder 1985	50 cents fixed co-payment per prescription	Full medicines coverage	USA, South Carolina Medicaid beneficiaries	Adrenergics Analgesics Antihistamines Anti-infectives Cardiovasculars Cholinergics Diuretics Gastrointestinals Psychotherapeutics Sedatives/Hypnotics Overall	Pharmacists could exempt patients from the co-payment	January 1, 1976-December 31, 1979
Roblin 2005	Increased cost sharing classified by level of increase: small ($1–$6), moderate ($7–$10) and large ($10)	Lower cost-sharing level	Enrollees of 5 managed care organizations (MCOs), USA	Hypoglycaemic medicines	Not reported	1997-2000
Sawyer 1982	50 cents fixed co-payment per prescription	Full medicines coverage (including most over-the-counter medicines)		Overall medicines	Restrictions on OTC medicines, on-	January 1974–December 1979

Table 13. Description of interventions: Fixed co-payment *(Continued)*

				ly insulin covered		

Table 14. Description of interventions: Tier + Fixed co-payment

Rev ID	Intervention	Comparision	Population	Medicines addressed in the paper	Exemptions/Modifiers	Intervention period
Hartung 2008	Co-pays for prescription medicines were set at $2 for generic and $3 for branded products	"Nominal" co-pays, of between $0.50 and $3	Users of Medicaid in Oregon, USA	Antidepressants, antipsychotics, inhaled beta-agonists, inhaled corticosteroids, inhaled anticholinergics, leukotriene modifiers, mast cell stabilisers, theophylline, diuretics, angiotension-converting enzyme inhibitors/receptor blockers, beta-blockers, alpha-blockers, digoxin, antiplatelets, aldosterone antagonists, insulin, sulfonylureas, nonsulfonylurea secretagogues, metformin, alpha-glucosidase inhibitors, thiazolidinediones and miscellaneous non-insulin injectables	Although co-pays were assessed, under federal law, providers were not allowed to deny services if the patient could not pay. In addition, $3 co-pays were set for outpatient services, including office visits, home visits, outpatient hospital services, outpatient surgery, outpatient treatment of chemical dependency, outpatient treatment for mental health, occupational and physical therapy, speech therapy, restorative dental work and vision exams	January 1, 2002-December 31, 2004
Huskamp 2007	Each plan switched from a 2-tier (generic and brand drugs) to a 3-tier formulary (generic, preferred and non-preferred brand drugs)	Under the 2-tier formularies used by each plan in the prepe-riod, the difference in co-payments for generic and brand medicines was only $5 or $10	Elderly, USA	Angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), calcium channel blockers (CCBs) and 3-hydroxy-3-methyl-glutaryl co-enzyme, a reductase inhibitor (statins), proton pump inhibitors (PPIs), selective serotonin-reuptake inhibitors (SSRIs) and non-steroidal anti-inflammatory drugs (NSAIDs))	The typical prescription filled through a retail outlet included a 30-day supply, and the typical prescription filled through the mail-order programme included a 90-day supply. Thus, enrollees had a financial incentive to use the mail-order programme in each plan	Distinct beginning and ending points, but at least 1 year before and 1 year after the intervention. The first before period observed was September 1999, and the last period observed was December 2002

Table 15. Description of interventions: Ceiling + Fixed co-payment

Rev ID	Intervention	Comparison	Population	Medicines addressed in the paper	Exemptions/Modifiers	Intervention period
Andersson 2006 (3)	Structure of co-payment changed for per dispensing occasion: maximum SEK 125 for 1 prescription + SEK 25 per additional prescription and increased annual co-payment maximum (SEK 1700)	Annual co-pay max SEK 1600	Swedish population	Indicators groups: (1) Acetic acid derivates and related substances (M01AB), a group of non-steroidal anti-inflammatory medicines (NSAIDs). Medicines in the group of acetic acid derivates could also be affected by RBP, as patents had expired when RBP was introduced in 1993 (2) Selective serotonin-re-uptake inhibitors, SSRIs (N06AB), a group of antidepressants	Not reported	January 1, 1993-December 31, 1996
Caetano 2006 (1)	Low-income elderly patients paid $10 per prescription for the first 20 prescriptions of the year, and other elderly patients (not low-income) paid $25 per prescription for the first 11 prescriptions. After this correspondent number of annual prescriptions was reached, prescriptions were free of charge	Comprehensive coverage for social assistance recipients and seniors, and fixed-deductible coverage for catastrophic medicines costs for all others	Residents of British Columbia, Vancouver, Canada	Statins and antihypertensives (including angiotensin-converting enzyme (ACE) inhibitors, angiotensin-II receptor blockers (ARBs), beta-blockers, calcium channel blockers (CCBs), alpha-antagonists, thiazide diuretics, non-thiazide diuretics and other antihypertensives (e.g. reserpine))	According to income level (higher-income households pay a larger share of private expenditures and/or receive a smaller share of available public subsidies)	January 1997 – April 2003
Dormuth 2006 (1)	Low-income elderly patients paid $10 per prescription for the first 20 prescriptions of the year, and other elderly patients (not low-income) paid $25 per prescription for the first 11 prescriptions. After this correspondent number of annual prescriptions was reached, prescriptions were free of charge	Comprehensive coverage for social assistance recipients and seniors, and fixed-deductible coverage for catastrophic medicines costs for all others	Elderly resident of British Columbia, Canada	Steroid, beta-2-agonist and anticholinergic	Those with age < 65 years who had received social income assistance were unaffected by policy changes	June 1997-May 2003

Table 15. Description of interventions: Ceiling + Fixed co-payment *(Continued)*

Dormuth 2008 (1)	Same as Dormuth 2006 (same study)	Same as Dormuth 2006 (same study)	Same as Dormuth 2006 (same study)	Inhaled medications for asthma	Those with age < 65 years who received social income assistance were unaffected by policy changes	Same as Dormuth 2006 (same study)
Dormuth 2009 (1)	Same as Dormuth 2006 (same study)	Same as Dormuth 2006 (same study)	Same as Dormuth 2006 (same study)	Steroids, beta-2-agonists and anticholinergics	Those with age < 65 years who received social income assistance were unaffected by policy changes	Same as Dormuth 2006 (same study)
Hynd 2008	Co-payments $4.60 for social security beneficiaries and $28.60 for general beneficiaries, and safety net thresholds of $239.20 for social security and $874.90 for general beneficiaries	Co-payments AUD $3.70 for social security beneficiaries and $23.10; safety net thresholds: $197.60 SS beneficiaries and $726.80 general beneficiaries	Australian Pharmaceutical Benefits Scheme (PBS) enrollees	Antiepileptics, antigout treatments, anti-Parkinson's treatments, anxiolytics, atypical antipsychotics, beta-blockers (indicated for heart failure rather than hypertension), combination asthma medicines, eyedrops, glaucoma treatments, hypnotics, insulin, muscle relaxants, non-aspirin antiplatelets, osteoporosis treatment, proton pump inhibitors (PPIs), statins and thyroxine	For those prescriptions priced below the co-payment amount, patients pay only the medicine cost (1) Safety net thresholds were increased by the equivalent costs of 2 prescriptions in January 2006 and January 2007 (2) A policy was introduced in January 2006 to exclude the early re-sup-	January 2000-September 2007

Table 15. Description of interventions: Ceiling + Fixed co-payment *(Continued)*

					ply of repeat prescriptions from the safety net. The normal supply of repeat PBS medicines includes 30 days of treatment, and under the new 'safety net 20 day rule', prescriptions re-supplied within 20 days no longer contributed towards a patient's safety net threshold, and were not supplied at the reduced co-payment once the threshold had been reached.	
Hynd 2009	Same as Hynd 2008 (same study)	Same as Hynd 2008 (same study)	Same as Hynd 2008 (same study)	Atypical antipsychotics, combination asthma, medicines, PPIs, statins	Same as Hynd 2008 (same study)	Same as Hynd 2008 (same study)
McManus 1996 (1)	Community: $15 fixed co-payment per presceription vs $11 fixed co-payment per prescription Elderly and social security: $2.5 fixed co-payment per prescription with ceiling at a "certain level" per year, after which medicines are free or available at reduced cost	Full medicines coverage	Australia population	Overall medicines (for chronic conditions) Symptomatic	Community: annual ceiling at a "certain" per year, after which medicines were free or available at reduced cost at	November 1990-September 1994

Table 15. Description of interventions: Ceiling + Fixed co-payment *(Continued)*

					both pre-policy and post-policy periods. Elderly/social security allowance to compensate for the introduction of co-payments and could be used freely	
McManus 1996 (2)	$2.50 fixed co-payment with ceiling at a "certain level" per year, after which medicines are free or available at reduced cost	Full medicines coverage	Australia population	Overall medicines (for chronic conditions) Symptomatic	Allowance to compensate for introduction of co-payments that can be freely used	
Poirier 1998	$2 fixed co-payment per prescription up to an annual $100 co-payment ceiling	Full medicines coverage	Canada	Antihypertensives Benzodiazepines	Pharmacists could discount or waive the co-payment, but must then cover the co-payment themselves. People eligible for income supplement (GIS) were exempted	May 1, 1991–December 31, 1993
Wang 2008b (1)	Same as Dormuth 2006 (same study).	Same as Dormuth 2006 (same study)	Same as Dormuth 2006 (same study)	Antidepressants	Same as Dormuth 2006 (same study)	Same as Dormuth 2006 (same study)

Table 16. Description of interventions: Ceiling + Co-insurance co-payment

Rev ID	Intervention	Comparison	Population	Medicines addressed in the paper	Exemptions/Modifiers	Intervention period
Andersson 2006 (4)	Patients pay 100% of the price up to SEK 400, 50% of the price between SEK 400 and SEK 1200, 25% of the price between SEK 1200 and SEK 2800 and 10% of the price between SEK 2800 and SEK 3800. Yearly maximum co-payment was SEK 1400 for pharmaceuticals	Structure of co-payment changed for per dispensing occasion: maximum SEK 125 for 1 prescription + SEK 25 per additional prescription and increased annual co-payment maximum (SEK 1700)	Swedish population	Indicators groups: (1) Acetic acid derivates and related substances (M01AB), a group of non-steroidal anti-inflammatory medicines (NSAIDs). Medicines in the group acetic acid derivatives could also be affected by RBP, as patents had expired when RBP was introduced in 1993 (2) Selective serotonin-reuptake inhibitors, SSRIs (N06AB), a group of antidepressants	Insulin was the only pharmaceutical group that continued to be free of charge after 1997	January 1, 1995-December 31, 1998
Andersson 2006 _(5)	Increased yearly co-payment maximum (SEK 1800) and adjusted levels within the scale (100% of the price up to SEK 900, 50% of the price between SEK 900 and SEK 1700, 25% of the price between SEK 1700 and SEK 3300 and 10% of the price between SEK 3300 and SEK 4300)	Patients pay 100% of the price up to SEK 400, 50% of the price between SEK 400 and SEK 1200, 25% of the price between SEK 1200 and SEK 2800 and 10% of the price between SEK 2800 and SEK 3800. Yearly maximum co-payment was SEK 1400 for pharmaceuticals	Swedish population	Indicators groups: (1) Acetic acid derivates and related substances (M01AB), a group of non-steroidal anti-inflammatory medicines (NSAIDs). Medicines in the group of acetic acid derivatives could also be affected by RBP, as patents had expired when RBP was introduced in 1993 (2) Selective serotonin-reuptake inhibitors, SSRIs (N06AB), a group of antidepressants	Insulin was the only pharmaceutical group that continued to be free of charge after 1997	January 1, 1997-December 31, 2002
Blais 2002 (1)	25% co-insurance up to an annual income-based $200, $500 or $750 co-payment ceiling	$2 fixed co-payment per perscription up to a $100 deductible	Low-income elderly in Quebec, Canada	Antihypertensives Anticoagulants Benzodiazepines Nitrates	Not reported	August 1996-December 1996
Blais 2002 (2)	25% co-insurance up to an	Full medicines coverage	Low-income el-	Inhaler corticosteroids Neuroleptics	Not reported	August 1996-De-

Table 16. Description of interventions: Ceiling + Co-insurance co-payment *(Continued)*

	annual $200 co-payment ceiling		derly in Quebec, Canada	Anticonvulsants		cember 1997
Caetano 2006 (2)	Fair PharmaCare IBD (income-based deductible) had 3 components: family deductible of 0% to 2% based on family income, co-insurance payment of 25% for prescriptions after passing the deductible and out-of-pocket ceiling equal to 1.25%, 2% or 3% of income. Families were responsible for all medicine costs under their deductible but may have had supplemental private insurance	Low-income elderly patients paid $10 per prescription for the first 20 prescriptions of the year, and other elderly patients (not low-income) paid $25 per prescription for the first 11 prescriptions. After this correspondent number of annual prescriptions was reached, prescriptions were free of charge	Residents of British Columbia, Vancouver, Canada	Statins and antihypertensives (including angiotensin-converting enzyme (ACE) inhibitors, angiotensin-II receptor blockers (ARBs), beta-blockers, calcium channel blockers (CCBs), alpha-antagonists, thiazide diuretics, non-thiazide diuretics and other antihypertensives (e.g. reserpine))	According to income level (higher-income households pay a larger share of private medicines expenditures and/or receive a smaller share of available public subsidies)	April 2003–December 2004
Dormuth 2006 (2)	Fair PharmaCare IBD (income-based deductible) had 3 components: family deductible of 0% to 2% based on family income, co-insurance payment of 25% for prescriptions after passing the deductible and out-of-pocket ceiling equal to 1.25%, 2% or 3% of income. Families were responsible for all medi-	Low-income elderly patients paid $10 per prescription for the first 20 prescriptions of the year, and other elderly patients (not low income) paid $25 per prescription for the first 11 prescriptions. After this correspondent number of annual prescriptions was reached, prescriptions were free of charge	Elderly residents of British Columbia, Canada	Asthma inhaler	Those with age < 65 years who received social income assistance were unaffected by policy changes Families were responsible for all medicines costs under their deductible but may have had supplemental private insurance	January 2002-June 2004

Table 16. Description of interventions: Ceiling + Co-insurance co-payment *(Continued)*

	cines costs under their deductible but may have had supplemental private insurance					
Dormuth 2008 (2)	Same as Dormuth 2006 (same study)	Same as Dormuth 2006 (same study)	Same as Dormuth 2006 (same study)	Asthma inhaler	Same as Dormuth 2006 (same study)	Same as Dormuth 2006 (same study)
Dormuth 2009 (2)	Fair PharmaCare IBD (income-based deductible) had 3 components: family deductible of 0% to 2% based on family income, co-insurance payment of 25% for prescriptions after passing the deductible and out-of-pocket ceiling equal to 1.25%, 2% or 3% of income. Families were responsible for all medicines costs under their deductible but may have had supplemental private insurance	Low-income elderly patients paid $10 per prescription for the first 20 prescriptions of the year, and other elderly patients (not low income) paid $25 per prescription for the first 11 prescriptions. After this correspondent number of annual prescriptions was reached, prescriptions were free of charge	Elderly residents of British Columbia, Canada	Asthma inhaler	Those with age < 65 years who received social income assistance were unaffected by policy changes	Same as Dormuth 2006 (same study)
Newhouse 1993	A: 25% co-insurance on medicines and inpatient/outpatient services up to an annual family income-based co-payment ceiling of 5/10% or 15%, or max $1000 B: 50% co-insurance on	Full medicines coverage	Non-elderly families	Prescription medicines	All participants were guaranteed not to be "worse off" than the previous plan and therefore in some cases were compensated by initiative payments (IPs)	1974-February 1977

Table 16. Description of interventions: Ceiling + Co-insurance co-payment *(Continued)*

	medicines and inpatient/outpatient services up to an annual family income-based co-payment ceiling of 5/10% or 15%, or max $1000 C: 95% co-insurance on medicines and inpatient/outpatient services up to an annual family income-based co-payment ceiling of 5/10% or 15%, or max $1000 D: 95% co-insurance on medicines and outpatient services, up to annual co-payment ceiling of $150 (individual) or $450 (family)					
Ong 2003 (2)	400 SEK fixed co-payment, after which patients pay a proportion of the additional cost up to an annual ceiling of 1300 SEK	160 initial fixed co-payment, after which patients pay 60 SEK for additional medicines	All outpatients from Stockholm, Sweden	Antidepressants Sedatives Anxiolytics	Not reported	July 1995-December 1999
Tamblyn 2001 (1)	25% co-insurance up to an annual income-based $200, $500 or $750 co-payment ceiling	$2 fixed co-payment per perscription up to a $100 deductible	Low-income elderly in Quebec, Canada	**Essential** (insulin, anticoagulants, ACE inhibitors, lipid-reducing medicines, antihypertensives, furosemide, beta-blockers, antiarrhythmics, aspirin, antiviral medicines, thyroid medicines, neuroleptics, antidepressants, anticonvulsants, antiparkinsonian medicines, prednisone, beta-agonists, inhaled steroids, chioroquines, primaquines, cyclosporine) **Less essential** (dipryridamole, probenicide, meperidine, benzodiazepines	Children and selected medicines groups were exempted from policy (medicines for STD and TB)	August 1996-December 1996

Table 16. Description of interventions: Ceiling + Co-insurance co-payment *(Continued)*

				(exluding clonazepam and clobazam))		
Tamblyn 2001 (2)	25% co-insurance up to an annual $200 co-payment ceiling	Full medicines coverage	Low-income elderly in Quebec, Canada	**Essential** (insulin, anticoagulants, ACE inhibitors, lipid-reducing medicines, antihypertensives, furosemide, beta-blockers, antiarrhythmics, aspirin, antiviral medicines, thyroid medicines, neuroleptics, antidepressants, anticonvulsants, antiparkinsonian medicines, prednisone, beta-agonists, inhaled steroids, chioroquines, primaquines, cyclosporine) **Less essential** (dipryridamole, probenicide, meperidine, benzodiazepines (excluding clonazepam and clobazam))	Children and selected medicines groups were exempted from policy (medicines for STD and TB)	August 1996-December 1996
Wang 2008b (2)	Same as Dormuth 2006 (same study)	Same as Dormuth 2006 (same study)	Same as Dormuth 2006 (same study)	Antidepressants	Same as Dormuth 2006 (same study)	Same as Dormuth 2006 (same study)

APPENDICES

Appendix 1. Search strategy of the original review

1.1. EMBASE

1. *Cost/
2. *Capitation Fee/
3. *Fee/
4. (cost? adj2 (share or shared or sharing)).tw.
5. (deductible? or coinsurance or co insurance).tw.
6. benefit plan?.tw.
7. capitation?.tw.
8. (cash adj1 pay$).tw.
9. ((charg$ or fee? or direct pay$ or direct contribut$) adj3 (patient? or prescrib$ or prescrip$ or pharmaceutic$ or pharmacy or pharmacies or dispens$)).tw.
10. (pocket? adj3 pay$).tw.
11. (copay$ or co pay$).tw.
12. ((limit$ or cap$ or restrict$ or reduc$ or regulat$) adj3 (prescrib$ or prescrip$ or reimburs$)).tw.
13. (tier or tiered system? or multitier$ or onetier$ or twotier$ or threetier$).tw.
14. single pay$.tw.
15. or/1-14
16. exp *Pharmaceutics/
17. exp *Drug/
18. *Prescription/
19. *"Drug Use"/
20. *Drug Utilization/
21. *Drug Cost/
22. (drug or drugs or pharmaceutic$ or medicines or medicament? or medicat$ or prescrib$ or prescrip$).tw.

23. or/16-22
24. Health Care Planning/
25. National Health Service/
26. Government/
27. Government Regulation/
28. Medicaid/
29. Medicare/
30. Health Maintenance Organization/
31. Health Care Policy/
32. Drug Legislation/
33. (regulat$ or requirement? or restrict$ or monitor$ or control$ or legislation? or law? or act? or policy or policies or reform$ or system? or plan$ or program$ or strateg$ or state$ or government? or medicaid or medicare or health maintenance organization? or hmo?).tw.
34. or/24-33
35. Randomized Controlled Trial/
36. (randomised or randomized).tw.
37. experiment$.tw.
38. Time Series Analysis/
39. (time adj series).tw.
40. (pre test or pretest or (posttest or post test)).tw.
41. impact.tw.
42. intervention?.tw.
43. chang$.tw.
44. evaluat$.tw.
45. effect?.tw.
46. Comparative Study/
47. compar$.tw.
48. or/35-47
49. Nonhuman/
50. letter.pt.
51. editorial.pt.
52. 48 not (49 or 50 or 51)
53. 15 and 23 and 34 and 52

1.2. Effective Practice and Organisation of Care Group Register

Effective Practice and Organisation of Care Group Register, Idealist database
Searched terms anywhere in text
cost sharing [or] deductible [or] deductibles [or] coinsurance [or] "co insurance" [or]
copay [or] co pay [or] cap

1.3. *The Cochrane Library* and CENTRAL

CENTRAL, The Cochrane Central Register of Controlled Trials, Ovid
Search fields: A combination of MeSH terms and text words
#1MeSH descriptor Cost Sharing, this term only
#2MeSH descriptor Deductibles and Coinsurance, this term only
#3MeSH descriptor Health Benefit Plans, Employee, this term only
#4MeSH descriptor Capitation Fee, this term only
#5MeSH descriptor Fees, Pharmaceutical, this term only
#6MeSH descriptor Fees and Charges, this term only
#7MeSH descriptor Prescription Fees, this term only
#8MeSH descriptor Single-Payer System, this term only
#9(cost* NEAR/2 (share or shared or sharing)):ti or (cost* NEAR/2 (share or shared or sharing)):ab
#10(deductible* or coinsurance or (co NEXT insurance)):ti or (deductible* or coinsurance or (co NEXT insurance)):ab
#11(benefit NEXT plan*):ti or (benefit NEXT plan*):ab
#12(capitation*):ti or (capitation*):ab
#13(cash NEAR/1 pay*):ti or (cash NEAR/1 pay*):ab
#14(charg* or fee* or (direct NEXT pay*) or (direct NEXT contribut*)) NEAR/3 (patient* or prescrib* or prescrip* or pharmaceutic* or pharmacy or pharmacies or dispens*):ti or (charg* or fee* or (direct NEXT pay*) or (direct NEXT contribut*)) NEAR/3 (patient* or prescrib* or prescrip* or pharmaceutic* or pharmacy or pharmacies or dispens*):ab
#15(pocket NEAR/3 pay*):ti or (pocket NEAR/3 pay*):ab
#16(copay* or (co NEXT pay*)):ti or (copay* or (co NEXT pay*)):ab

#17(limit* or cap* or restrict* or reduce* or regulat*) NEAR/3 (prescrib* or prescrip* or reimburse*):ti or (limit* or cap* or restrict* or reduce* or regulat*) NEAR/3 (prescrib* or prescrip* or reimburse*):ab
#18(tier or (tiered NEXT system*) or multitier* or onetier* or twotier* or threetier*):ti or (tier or (tiered NEXT system*) or multitier* or onetier* or twotier* or threetier*):ab
#19(single NEXT pay*):ti or (single NEXT pay*):ab
#20(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19)
#21MeSH descriptor Pharmaceutical Preparations explode all trees
#22MeSH descriptor Prescriptions, Drug, this term only
#23MeSH descriptor Drug Utilization, this term only
#24MeSH descriptor Drug Costs, this term only
#25(drug or drugs or pharmaceutic* or medicines or medicament* or medicat* or prescrib* or prescrip*):ti or (drug or drugs or pharmaceutic* or medicines or medicament* or medicat* or prescrib* or prescrip*):ab
#26(#21 OR #22 OR #23 OR #24 OR #25)
#27MeSH descriptor State Health Plans, this term only
#28MeSH descriptor State Medicine, this term only
#29MeSH descriptor Government Programs, this term only
#30MeSH descriptor National Health Programs, this term only
#31MeSH descriptor Medicaid, this term only
#32MeSH descriptor Medicare, this term only
#33MeSH descriptor Health Maintenance Organizations, this term only
#34MeSH descriptor Health Policy, this term only
#35MeSH descriptor Health Care Reform, this term only
#36MeSH descriptor Policy Making, this term only
#37MeSH descriptor Legislation, Drug, this term only
#38(regulat* or requirement* or restrict* or monitor* or control* or legislation* or law* or act* or policy or policies or reform* or system* or plan* or program* or strateg* or state* or government* or medicaid or medicare or (health NEXT maintenance NEXT organi*ation*) or hmo or hmos):ti or (regulat* or requirement* or restrict* or monitor* or control* or legislation* or law* or act* or policy or policies or reform* or system* or plan* or program* or strateg* or state* or government* or medicaid or medicare or (health NEXT maintenance NEXT organi*ation*) or hmo or hmos):ab
#39(#27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38)
#40(#20 AND #26 AND #39)

1.4. CSA Worldwide Political Science Abstracts

CSA Worldwide Political Science Abstracts
Search field: 'Key Words'
KW=(legislation OR law* OR act* OR policy OR policies OR politics OR reform* OR system* OR plan* program* OR strateg* OR regulat* OR requirement* OR restrict* OR monitor* OR control)
AND
KW=(drug* OR pharmaceutic* OR medicines OR medicament* OR medicat*)
AND
KW=(random* OR intervention* OR control* OR compar* OR evaluat* OR time OR longitud* OR repeated measure* OR pretest OR posttest OR pre test OR post test OR impact* OR chang* OR effect* OR experiment*)

1.5. EconLit

EconLit, WebSPIRS
Search filed: 'Terms Anywhere'
regulat* or requirement or restrict* or monitor* or control* or legislation or law? or act? or policy or policies or politics or reform* or system? or plan* or program? or strateg*)
and
(drug? or pharmaceutic* or medicines or medicament? or medicat*)
and
(random* or intervention? or control* or compar* or evaluat* or time or pretest or posttest or pre test or post test or impact? or chang* or effect? or experiment?)

1.6. SIGLE

SIGLE, System for Information on Grey Literature in Europe, WebSPIRS
Search field: 'Terms Anywhere'
(regulat* or requirement or restrict* or monitor* or control* or legislation or law? or act? or policy or policies or politics or reform* or system? or plan* or program? or strateg*)
and

(drug? or pharmaceutic* or medicines or medicament? or medicat*)
and
(random* or intervention? or control* or compar* or evaluat* or time or pretest or posttest or pre test or post test or impact? or chang* or effect? or experiment?)

1.7. INRUD

INRUD, International Network for Rational Use of Drugs
Search field: 'All non-indexed fields'
{drug} or {pharmaceutic} or {medicines} or {medicament} or {medicat}
AND
{regulat} or {requirement} or {restrict} or {monitor} or {control} or {legislation} or {law} or {act} or {policy} or {policies} or {politics} or {reform} or {system} or {plan} or {program} or {strateg}
AND
{random} or {intervention} or {control} or {compar} or {evaluat} or {time} or {pretest} or {posttest} or {pre test} or {post test} or {impact} or {chang} or {effect} or {experiment}

1.8. PAIS International

PAIS International, Public Affairs Information Service, WebSPIRS
Search fields: 'Descriptors' or 'Title' or 'Abstract'
1.
((explode "Drug-stores" in DE) or (explode "Pharmacists" in DE) or (explode "Prescriptions" in DE) or (explode "Drugs" in DE) or (explode "Pharmaceutical-industry" in DE)
OR
((((drug? or pharmaceutic* or medicines or medicament? or medicat*)) in AB)
OR
(((drug? or pharmaceutic* or medicines or medicament? or medicat*)) in TI)))
AND
((((random* or intervention? or control* or compar* or evaluat* or time or pretest or posttest or pre test or post test or impact? or chang* or effect? or experiment?)) in AB)
OR
(((random* or intervention? or control* or compar* or evaluat* or time or pretest or posttest or pre test or post test or impact? or chang* or effect? or experiment?)) in TI))
AND
((((regulat* or requirement or restrict* or monitor* or control* or legislation or law? or act? or policy or policies or politics or reform* or system? or plan* or program? or strateg*)) in AB)
OR
(((regulat* or requirement or restrict* or monitor* or control* or legislation or law? or act? or policy or policies or politics or reform* or system? or plan* or program? or strateg*)) in TI))
2.
((narco* or crim* or war? or terror* or weapon? or addict* or abus* or traffic* or illicit*) in AB)
OR
((narco* or crim* or war? or terror* or weapon? or addict* or abus* or traffic* or illicit*) in TI)
3.
(1 AND 2) NOT 3

1.9. International Political Science Abstracts

International Political Science Abstracts, WebSPIRS
Search field: 'Terms Anywhere'
(regulat* or requirement or restrict* or monitor* or control* or legislation or law? or act? or policy or policies or politics or reform* or system? or plan* or program? or strateg*)
and
(drug? or pharmaceutic* or medicines or medicament? or medicat*)
and
(random* or intervention? or control* or compar* or evaluat* or time or pretest or posttest or pre test or post test or impact? or chang* or effect? or experiment?)

1.10. NHS EED

NHS EED, National Health Services Economic Evaluation Database, CRD
Search fields: A combination of 'Subject Headings' and 'All fields'

Search done in 6 separate stages
#1MeSH descriptor Cost Sharing, this term only
#2MeSH descriptor Deductibles and Coinsurance, this term only
#3MeSH descriptor Health Benefit Plans, Employee, this term only
#4MeSH descriptor Capitation Fee, this term only
#5MeSH descriptor Fees, Pharmaceutical, this term only
#6MeSH descriptor Fees and Charges, this term only
#7MeSH descriptor Prescription Fees, this term only
#8MeSH descriptor Single-Payer System, this term only
#9(cost* NEAR/2 (share or shared or sharing)):ti or (cost* NEAR/2 (share or shared or sharing)):ab
#10(deductible* or coinsurance or (co NEXT insurance)):ti or (deductible* or coinsurance or (co NEXT insurance)):ab
#11(benefit NEXT plan*):ti or (benefit NEXT plan*):ab
#12(capitation*):ti or (capitation*):ab
#13(cash NEAR/1 pay*):ti or (cash NEAR/1 pay*):ab
#14(charg* or fee* or (direct NEXT pay*) or (direct NEXT contribut*)) NEAR/3 (patient* or prescrib* or prescrip* or pharmaceutic* or pharmacy or pharmacies or dispens*):ti or (charg* or fee* or (direct NEXT pay*) or (direct NEXT contribut*)) NEAR/3 (patient* or prescrib* or prescrip* or pharmaceutic* or pharmacy or pharmacies or dispens*):ab
#15(pocket NEAR/3 pay*):ti or (pocket NEAR/3 pay*):ab
#16(copay* or (co NEXT pay*)):ti or (copay* or (co NEXT pay*)):ab
#17(limit* or cap* or restrict* or reduce* or regulat*) NEAR/3 (prescrib* or prescrip* or reimburse*):ti or (limit* or cap* or restrict* or reduce* or regulat*) NEAR/3 (prescrib* or prescrip* or reimburse*):ab
#18(tier or (tiered NEXT system*) or multitier* or onetier* or twotier* or threetier*):ti or (tier or (tiered NEXT system*) or multitier* or onetier* or twotier* or threetier*):ab
#19(single NEXT pay*):ti or (single NEXT pay*):ab
#20(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19)
#21MeSH descriptor Pharmaceutical Preparations explode all trees
#22MeSH descriptor Prescriptions, Drug, this term only
#23MeSH descriptor Drug Utilization, this term only
#24MeSH descriptor Drug Costs, this term only
#25(drug or drugs or pharmaceutic* or medicines or medicament* or medicat* or prescrib* or prescrip*):ti or (drug or drugs or pharmaceutic* or medicines or medicament* or medicat* or prescrib* or prescrip*):ab
#26(#21 OR #22 OR #23 OR #24 OR #25)
#27MeSH descriptor State Health Plans, this term only
#28MeSH descriptor State Medicine, this term only
#29MeSH descriptor Government Programs, this term only
#30MeSH descriptor National Health Programs, this term only
#31MeSH descriptor Medicaid, this term only
#32MeSH descriptor Medicare, this term only
#33MeSH descriptor Health Maintenance Organizations, this term only
#34MeSH descriptor Health Policy, this term only
#35MeSH descriptor Health Care Reform, this term only
#36MeSH descriptor Policy Making, this term only
#37MeSH descriptor Legislation, Drug, this term only
#38(regulat* or requirement* or restrict* or monitor* or control* or legislation* or law* or act* or policy or policies or reform* or system* or plan* or program* or strateg* or state* or government* or medicaid or medicare or (health NEXT maintenance NEXT organi*ation*) or hmo or hmos):ti or (regulat* or requirement* or restrict* or monitor* or control* or legislation* or law* or act* or policy or policies or reform* or system* or plan* or program* or strateg* or state* or government* or medicaid or medicare or (health NEXT maintenance NEXT organi*ation*) or hmo or hmos):ab
#39(#27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38)
#40(#20 AND #26 AND #39)

1.11. NTIS

NTIS, National Technical Information service
Search fields: A combination of 'Index Terms' (KT), 'Key Words/Phrases' (no tag) and 'Title'
#1. KT=PHARMACEUTICALS OR KT=DRUGS OR KT=MEDICATIONS OR KT= PRESCRIPTION DRUGS OR KT=DRUG #PRESCRIPTIONS
#2. REGULAT* OR REQUIR* OR RESTRICT* OR LEGISLAT* OR LAW? OR ACT? OR POLICY OR POLICIES
#3. COMPAR* OR EVALUAT* OR EFFECT?
#4. NARCO* OR CRIM* OR WAR? OR ADDICT* OR ABUS* OR TRAFFIC* OR ILLICIT*
#5. TI=MANUAL? OR TI=CANCER OR TI=REGISTRATION FILE OR TI=RETIRED REGISTRANTS
#6. (#1 AND #2 AND #3) NOT #4
#7. #6 NOT #5

1.12. IPA

IPA, International Pharmaceutical Abstract, WebSPIRS
Search fields: A combination of 'Descriptors' and 'Terms Anywhere'
1.
((approval*) in DE) or ((licensing) in DE) or ((licensure) in DE) or ((labeling) in DE) or ((classification) in DE) or ((patent*) in DE) or ((marketing) in DE) or ((advertising) in DE) or ((insurance) in DE) or ((reimbursement) in DE) or ((formularies) in DE) or ((formulary) in DE) or ((essential) in DE) or (reminder system*) or ((Education-pharmaceutical-continuing) in DE) or ((Education-continuing) in DE) or ((Hospitals-pharmacy-and-therapeutics-committee) in DE) or (drug* near1 monitoring) or ((Drugs-adverse-reactions-reports) in DE) or ((Reports-drugs-adverse-reactions) in DE) or ((Costs-drugs) in DE) or ((Pricing-drugs) in DE) or ((pharmacoeconomics) in DE) or (reference near2 pric*) or ((Costs-prescription-drugs) in DE) or ((purchasing) in DE) or (cost adj sharing) or ((copayment*) in DE) or (deductibles) or (coinsurance) or ((drug information services) in DE) or (patient adj education)
2.
(regulat* or restrict* or control* or legislat* or law or laws or act or acts or policy or policies or program or programs) and (control* or compar* or evaluat* or time series or impact* or effect or effects) and ((sc=20) or (sc=22))
3.
(1 and 2) not sc=6

1.13. OECD

OECD (Organisation for Economic Co-operation and Development)
Searched: Publications & Documents, limited to OECD Publications only
drug or drugs or pharmaceutical or pharmaceuticals or medicaments or medicines or prescription or prescriptions or prescribe or prescribing

1.14. SourceOECD

SourceOECD
Search fields: 'Title' or 'Abstract'
drug or drugs or pharmaceutic* or medicament* or medicines or prescrip*or prescrib*

1.15. World Bank Documents & Reports

World Bank Documents & Reports
Limited to sectors: Health, Nutrition and Population or Hospitals, Secondary & Tertiary or Primary health or Reform and Financing
drug or drugs or pharmaceutical or pharmaceuticals or medicament or medicaments or medicines or prescription or prescriptions or prescribe or prescribed or prescribing

1.16. World Bank e-Library

World Bank e-Library
Search fields: 'Title' or 'Abstract' or 'Keywords'
drug or drugs or pharmaceutical or pharmaceuticals or pharmaceutic or pharmaceutics or medicament or medicaments or medicines or prescription or prescriptions or prescribe or prescribed or prescribing

1.17. JOLIS

1.
keywords anywhere "copay$ or co adj pay$ or caps or deductible$ or coinsur$ or co adj insur$ or cost adj sharing or capitation or benefit adj plan$" AND keywords anywhere "drug or drugs or pharmaceutic$ or medicament$ or medicines or prescrip$ or prescrib$" search found 5 titles.
2.
keywords anywhere "pocket adj pay$ or patient$ adj pay$ or direct adj pay$ or cash adj pay$ or tier or tiered adj system$ or multitier or onetier or twotier or threetier or single adj pay$" AND keywords anywhere "drug or drugs or pharmaceutic$ or medicament$ or medicines or prescrip$ or prescrib$" found no matches in any library.
3.
keywords anywhere "limit$ or cap or caps or restrict$ or reduce$ or regulat$" AND keywords anywhere "prescript$ or prescribe$ or reimburse$" search found 43 titles.
4.
keywords anywhere "prescrib$ or prescrip$ or pharmaceutic$ or pharmacy or pharmacies or dispens$ or patient$" AND keywords anywhere "charg$ or fee or fees" search found 13 titles.

1.18. Global JOLIS

1.
words or phrase "copay$ or co adj pay$ or caps or deductible$ or coinsur$ or co adj insur$"
AND
words or phrase "drug or drugs or pharmaceutic$ or medicament$ or medicines or prescrip$ or prescrib$"
2.
words or phrase "cost adj sharing or capitation or benefit adj plan$"
AND
words or phrase "drug or drugs or pharmaceutic$ or medicament$ or medicines or prescrip$ or prescrib$"
3.
words or phrase "pocket adj pay$ or patient$ adj pay$ or direct adj pay$ or cash adj pay$"
AND
words or phrase "drug or drugs or pharmaceutic$ or medicament$ or medicines or prescrip$ or prescrib$"
4.
words or phrase "tier or tiered adj system$ or multitier or onetier or twotier or threetier or single adj pay$"
AND
words or phrase "drug or drugs or pharmaceutic$ or medicament$ or medicines or prescrip$ or prescrib$"
5.
words or phrase "limit$ or cap or caps or restrict$ or reduce$ or regulat$"
AND
words or phrase "prescrip$ or prescrib$ or reimburse$"
6.
words or phrase "prescrib$ or prescrip$ or pharmaceutic$ or pharmacy or pharmacies or dispens$ or patient$"
AND
words or phrase "charg$ or fee or fees"

1.19. WHO

WHO (World Health Organisation),
Browsed The Essential Drugs and Medicines web site

1.20. WHOLIS

Search field: 'Words or phrase'
Search done in 4 separate stages.

1.words or phrase "copay$ or co adj pay$ or caps or deductible$ or coinsur$ or co adj insur$ or cost adj sharing or capitation or benefit adj plan$ or pocket adj pay$ or patient$ adj pay$ or direct adj pay$ or cash adj pay$"
AND
words or phrase "drug or drugs or pharmaceutic$ or medicament$ or medicines or prescrip$ or prescrib$"
2.
words or phrase "tier or tiered adj system$ or multitier or onetier or twotier or threetier or single adj pay$"
AND
words or phrase "drug or drugs or pharmaceutic$ or medicament$ or medicines or prescrip$ or prescrib$"
3.
words or phrase "limit$ or cap or caps or restrict$ or reduce$ or regulat$"
AND
words or phrase "prescrip$ or prescrib$ or reimburse$"
4.
words or phrase "prescrib$ or prescrip$ or pharmaceutic$ or pharmacy or pharmacies or dispens$ or patient$" AND
words or phrase "charg$ or fee or fees"

Appendix 2. Search strategies: *The Cochrane Library* and CENTRAL

#1 MeSH descriptor: [Cost Sharing] this term only

#2 MeSH descriptor: [Deductibles and Coinsurance] this term only

#3 MeSH descriptor: [Health Benefit Plans, Employee] this term only

#4 MeSH descriptor: [Capitation Fee] this term only

#5 MeSH descriptor: [Fees, Pharmaceutical] this term only

#6 MeSH descriptor: [Fees and Charges] this term only

#7 MeSH descriptor: [Prescription Fees] this term only

#8 MeSH descriptor: [Single-Payer System] this term only

#9 (cost* near/2 (share or shared or sharing)):ti,ab,kw

#10 (deductible* or coinsurance or (co next insurance)):ti,ab,kw

#11 (benefit next plan*):ti,ab,kw

#12 (capitation*):ti,ab,kw

#13 (cash near/1 pay*):ti,ab,kw

#14 (charg* or fee or fees or (direct next pay*) or (direct next contribut*)) near/3 (patient* or prescrib* or prescrip* or pharmaceutic* or pharmacy or pharmacies or dispens*):ti,ab,kw

#15 (pocket near/3 pay*):ti,ab,kw

#16 (copay* or (co next pay*)):ti,ab,kw

#17 (limit* or cap or caps or capitat* or restrict* or reduce* or regulat*) near/3 (prescrib* or prescrip* or reimburse*):ti,ab,kw

#18 (tier or (tiered next system*) or multitier* or onetier* or twotier* or threetier*):ti,ab,kw

#19 (single next pay*):ti,ab,kw

#20 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19

#21 MeSH descriptor: [Pharmaceutical Preparations] explode all trees

#22 MeSH descriptor: [Drug Prescriptions] this term only

#23 MeSH descriptor: [Drug Utilization] this term only

#24 MeSH descriptor: [Drug Costs] this term only

#25 (drug or drugs or pharmaceutic* or medicines or medicament* or medicat* or prescrib* or prescrip*):ti,ab,kw

#26 #21 or #22 or #23 or #24 or #25

#27 MeSH descriptor: [State Health Plans] this term only

#28 MeSH descriptor: [State Medicine] this term only

#29 MeSH descriptor: [Government Programs] this term only

#30 MeSH descriptor: [National Health Programs] this term only

#31 MeSH descriptor: [Medicaid] this term only

#32 MeSH descriptor: [Medicare] this term only

#33 MeSH descriptor: [Health Maintenance Organizations] this term only

#34 MeSH descriptor: [Health Policy] this term only

#35 MeSH descriptor: [Health Care Reform] this term only

#36 MeSH descriptor: [Policy Making] this term only

#37 MeSH descriptor: [Legislation, Drug] this term only

#38 (regulat* or requirement* or restrict* or monitor* or control* or legislation* or law or laws or act or acts or policy or policies or reform* or system* or plan* or program* or strateg* or state* or government* or medicaid or medicare or (health next maintenance next organi*ation*) or hmo or hmos):ti,ab,kw

#39 #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38

#40 #20 and #26 and #39 in Cochrane Reviews (Reviews only)

#40 #20 and #26 and #39 in Cochrane Reviews (Protocols only)

#40 #20 and #26 and #39 in Other Reviews

#40 #20 and #26 and #39 in Trials

#40 #20 and #26 and #39 in Technology Assessments

#40 #20 and #26 and #39 in Economic Evaluations

Appendix 3. Search strategy: MEDLINE In-Process & Other Non-Indexed Citations (Ovid)

Searches

1 *Cost Sharing/

2 *"Deductibles and Coinsurance"/

3 *Health Benefit Plans, Employee/

4 *Capitation Fee/

5 *Fees, Pharmaceutical/

6 *"Fees and Charges"/

7 *Prescription Fees/

8 *Single-Payer System/

9 (cost? adj2 (share or shared or sharing)).tw.

10 (deductible? or coinsurance or co insurance).tw.

11 benefit plan?.tw.

12 capitation?.tw.

13 (cash adj1 pay$).tw.

14 ((charg$ or fee? or direct pay$ or direct contribut$) adj3 (patient? or prescrib$ or prescrip$ or pharmaceutic$ or pharmacy or pharmacies or dispens$)).tw.

15 (pocket adj3 pay$).tw.

16 (copay$ or co pay$).tw.

17 ((limit$ or cap$ or restrict$ or reduc$ or regulat$) adj3 (prescrib$ or prescrip$ or reimburs$)).tw.

18 (tier or tiered system? or multitier$ or onetier$ or twotier$ or threetier$).tw.

19 single pay$.tw.

20 or/1-19

21 exp *Pharmaceutical Preparations/

22 *Drug Prescriptions/

23 *Drug Utilization/

24 *Drug Costs/

25 (drug or drugs or pharmaceutic$ or medicines or medicament? or medicat$ or prescrib$ or prescrip$).tw.

26 or/21-25

27 State Health Plans/

28 State Medicine/

29 Government Programs/

30 National Health Programs/

31 Medicaid/

32 Medicare/

33 Health Maintenance Organizations/

34 Health Policy/

35 Health Care Reform/

36 Policy Making/

37 Legislation, Drug/

38 (regulat$ or requirement? or restrict$ or monitor$ or control$ or legislation? or law? or act? or policy or policies or reform$ or system? or plan$ or program$ or strateg$ or state$ or government? or medicaid or medicare or health maintenance organi#ation? or hmo?).tw.

39 or/27-38

40 20 and 26 and 39

Appendix 4. Search strategy: MEDLINE (Ovid)

Searches

1 *Cost Sharing/

2 *"Deductibles and Coinsurance"/

3 *Health Benefit Plans, Employee/

4 *Capitation Fee/

5 *Fees, Pharmaceutical/

6 *"Fees and Charges"/

7 *Prescription Fees/

8 *Single-Payer System/

9 (cost? adj2 (share or shared or sharing)).tw.

10 (deductible? or coinsurance or co insurance).tw.

11 benefit plan?.tw.

12 capitation?.tw.

13 (cash adj1 pay$).tw.

14 ((charg$ or fee? or direct pay$ or direct contribut$) adj3 (patient? or prescrib$ or prescrip$ or pharmaceutic$ or pharmacy or pharmacies or dispens$)).tw.

15 (pocket adj3 pay$).tw.

16 (copay$ or co pay$).tw.

17 ((limit$ or cap$ or restrict$ or reduc$ or regulat$) adj3 (prescrib$ or prescrip$ or reimburs$)).tw.

18 (tier or tiered system? or multitier$ or onetier$ or twotier$ or threetier$).tw.

19 single pay$.tw.

20 or/1-19

21 exp *Pharmaceutical Preparations/

22 *Drug Prescriptions/

23 *Drug Utilization/

24 *Drug Costs/

25 (drug or drugs or pharmaceutic$ or medicines or medicament? or medicat$ or prescrib$ or prescrip$).tw.

26 or/21-25

27 State Health Plans/

28 State Medicine/

29 Government Programs/

30 National Health Programs/

31 Medicaid/

32 Medicare/

33 Health Maintenance Organizations/

34 Health Policy/

35 Health Care Reform/

36 Policy Making/

37 Legislation, Drug/

38 (regulat$ or requirement? or restrict$ or monitor$ or control$ or legislation? or law? or act? or policy or policies or reform$ or system? or plan$ or program$ or strateg$ or state$ or government? or medicaid or medicare or health maintenance organi#ation? or hmo?).tw.

39 or/27-38

40 20 and 26 and 39

41 randomized controlled trial.pt.

42 controlled clinical trial.pt.

43 intervention studies/

44 experiment$.tw.

45 (time adj series).tw.

46 (pre test or pretest or (posttest or post test)).tw.

47 random allocation/

48 impact.tw.

49 intervention?.tw.

50 chang$.tw.

51 effect?.tw.

52 evaluation studies/

53 evaluat$.tw.

54 comparative studies/

55 (randomized or randomised).tw.

56 (random$ adj1 (allocat$ or assign$)).tw.

57 or/41-56

58 comment.pt.

59 editorial.pt.

60 review.pt.

61 comment on.cm.

62 "cochrane database of systematic reviews".jn.

63 exp animals/ not humans.sh.

64 or/58-63

65 57 not 64

66 40 and 65

67 (2006* or 2007* or 2008* or 2009* or 2010* or 2011*).ed,ep,dp,yr.

68 (201110* or 201111* or 201112* or 2012* or 2013*).ed.

69 66 and 67 and 68

Appendix 5. Search strategy: EMBASE (Ovid)

Searches

1 *Cost/

2 *Capitation Fee/

3 *Fee/

4 (cost? adj2 (share or shared or sharing)).tw.

5 (deductible? or coinsurance or co insurance).tw.

6 benefit plan?.tw.

7 capitation?.tw.

8 (cash adj1 pay$).tw.

9 ((charg$ or fee? or direct pay$ or direct contribut$) adj3 (patient? or prescrib$ or prescrip$ or pharmaceutic$ or pharmacy or pharmacies or dispens$)).tw.

10 (pocket? adj3 pay$).tw.

11 (copay$ or co pay$).tw.

12 ((limit$ or cap$ or restrict$ or reduc$ or regulat$) adj3 (prescrib$ or prescrip$ or reimburs$)).tw.

13 (tier or tiered system? or multitier$ or onetier$ or twotier$ or threetier$).tw.

14 single pay$.tw.

15 or/1-14

16 exp *Pharmaceutics/

17 exp *Drug/

18 *Prescription/

19 *"Drug Use"/

20 *Drug Utilization/

21 *Drug Cost/

22 (drug or drugs or pharmaceutic$ or medicines or medicament? or medicat$ or prescrib$ or prescrip$).tw.

23 or/16-22

24 *Health Care Planning/

25 *National Health Service/

26 *Government/

27 *Government Regulation/

28 *Medicaid/

29 *Medicare/

30 *Health Maintenance Organization/

31 *Health Care Policy/

32 *Drug Legislation/

33 (regulat$ or requirement? or restrict$ or monitor$ or control$ or legislation? or law? or act? or policy or policies or reform$ or system? or plan$ or program$ or strateg$ or state$ or government? or medicaid or medicare or health maintenance organization? or hmo?).tw.

34 or/24-33

35 Randomized Controlled Trial/

36 (randomised or randomized).tw.

37 experiment$.ti.

38 Time Series Analysis/

39 (time adj series).tw.

40 (pre test or pretest or (posttest or post test)).tw.

41 impact.ti.

42 intervention?.ti.

43 chang$.tw.

44 evaluat$.ti.

45 effect?.ti.

46 Comparative Study/

47 compar$.ti.

48 or/35-47

49 Nonhuman/

50 editorial.pt.

51 "cochrane database of systematic reviews".jn.

52 review.ti.

53 48 not (49 or 50 or 51 or 52)

54 15 and 23 and 34 and 53

55 limit 54 to embase

56 (2011* or 2012* or 2013*).em.

57 (2006* or 2007* or 2008* or 2009* or 2010* or 2011*).em.

58 55 and 56 and 57

Appendix 6. Search strategy: International Political Science Abstracts (IPSA) (EBSCO)

S7 (S4 and S5 and S6)

S6 TX (randomis* or randomiz* or randomly or intervention* or control* or compar* or evaluat* or "time series" or pretest or posttest or "pre test" or "post test" or impact or chang* or effect* or experiment*)

S5 TX (drug or drugs or pharmaceutic* or medicin* or medicament* or medicat* or prescrib* or prescrip* or health*)

S4 (S1 or S2 or S3)

S3 TX (capitat* or prescrip* or prescrib* or drug or drugs or pharmaceutic* or medical) N3 (fee or fees or charg*)

S2 TX (cost or expenditure or expens* or spend* or benefit) N3 (cap or caps)

S1 TX (cost N1 shar* or copay* or co W0 pay* or coinsurance or "co insurance" or deductible* or "benefit plan" or "benefit plans" or drug N3 benefit* or drugs N3 benefit* or "user fee" or "user fees" or "out of pocket" or tier or "tiered system" or "tiered systems" or multitier or onetier or twotier or threetier)

Appendix 7. Search strategy: EconLit (ProQuest); Worldwide Political Science Abstracts (ProQuest); and PAIS International (ProQuest)

All(cost NEAR/0 shar* OR copay* OR co PRE/0 pay* OR coinsurance OR "co insurance" OR deductible* OR "benefit plan" OR "benefit plans" OR drug NEAR/3 benefit* OR drugs NEAR/3 benefit* OR "user fee" OR "user fees" OR capitat* PRE/0 fee OR capitat* PRE/0 fees OR cost NEAR/3 cap OR cost NEAR/3 caps OR expenditure NEAR/3 cap OR expenditure NEAR/3 caps OR expens* NEAR/3 cap OR expens* NEAR/3 caps OR spend* NEAR/3 cap OR spend* NEAR/3 caps OR benefit NEAR/3 cap OR benefit NEAR/3 caps OR prescrip* NEAR/3 fee OR prescrip* NEAR/3 fees OR prescrib* NEAR/3 fee OR prescrib* NEAR/3 fees OR drug NEAR/3 fee OR drug NEAR/3 fees OR drugs NEAR/3 fee OR drugs NEAR/3 fees OR pharmaceutic* NEAR/3 fee OR pharmaceutic* NEAR/3 fees OR medical NEAR/3 fee OR medical NEAR/3 fees OR prescrip* NEAR/3 charg* OR prescrib* NEAR/3 charg* OR drug NEAR/3 charg* OR drugs NEAR/3 charg* OR pharmaceutic* NEAR/3 charg* OR medical NEAR/3 charg* OR "out of pocket" OR tier OR "tiered system" OR "tiered systems" OR multitier OR onetier OR twotier OR threetier) AND ALL(drug OR drugs OR pharmaceutic* OR medicin* OR medicament* OR medicat* OR prescrib* OR prescrip*) AND ALL(randomis* OR randomiz* OR randomly OR intervention* OR control* OR compar* OR evaluat* OR "time series" OR pretest OR posttest OR "pre test" OR "post test" OR impact OR chang* OR effect* OR experiment*)

Appendix 8. Search strategy: INRUD Bibliography

(Search field: All Non-Indexed Text Files)

{cost shar} or {copay} or {co pay} or {coinsurance} or {co insurance} or {deductible} or {benefit plan} or {drug benefit} or {user fee} or {capitation fee} or {capitated fee} or {prescription fee} or {drug fee} or {pharmaceutical fee} or {medical fee} or {prescription charg} or {drug charg} or {pharmaceutical charg} or {medical charg} or {cost cap} or {expenditure cap} or {benefit cap} or {out of pocket} or {tier} or {multitier} or {onetier} or {twotier} or {threetier}
AND
{randomis} or {randomiz} or {randomly} or {intervention} or {control} or {compar} or {evaluat} or {time series} or {pretest} or {posttest} or {pre test} or {post test} or {impact} or {chang} or {effect} or {experiment}

Appendix 9. Search strategy: WHOLIS (VHL)

((MH:"Cost Sharing" OR "Deductibles and Coinsurance" OR "Health Benefit Plans, Employee" OR "Capitation Fee" OR "Fees, Pharmaceutical" OR "Fees and Charges" OR "Prescription Fees" OR "Single-Payer System") OR (TI:"cost sharing" OR copayment* OR "co payment" OR "co payments" OR coinsurance OR "co insurance" OR deductible* OR "tiered system" OR "tiered systems" OR multitier OR "multi tier" OR onetier OR "one tier" OR "1 tier" OR twotier OR "two tier" OR "2 tier" OR threetier OR "three tier" OR "3 tier") OR (AB:"cost sharing" OR copayment* OR "co payment" OR "co payments" OR coinsurance OR "co insurance" OR deductible* OR "tiered system" OR "tiered systems" OR multitier OR "multi tier" OR onetier OR "one tier" OR "1 tier" OR twotier OR "two tier" OR "2 tier" OR threetier OR "three tier" OR "3 tier")) AND ((MH:"Pharmaceutical Preparations" OR "Drug Prescriptions" OR "Drug Utilization" OR "Drug Costs") OR (TI:drug OR drugs OR pharmaceutic* OR medicines OR medication) OR (AB:drug OR drugs OR pharmaceutic* OR medicines OR medication)) AND ((PT:"Randomized controlled trial" OR "Controlled clinical trial") OR (MH:Intervention Study OR Evaluation Study OR Comparative Study) OR (TI:randomis* OR randomiz* OR randomly OR intervention* OR control* OR compar* OR evaluat* OR "time series" OR pretest OR posttest OR "pre test" OR "post test" OR impact OR chang* OR effect* OR experiment*) OR (AB:randomis* OR randomiz* OR randomly OR intervention* OR control* OR compar* OR evaluat* OR "time series" OR pretest OR posttest OR "pre test" OR "post test" OR impact OR chang* OR effect* OR experiment*))

Appendix 10. Search strategy: LILACS (VHL)

((MH:"Cost Sharing" OR "Deductibles and Coinsurance" OR "Health Benefit Plans, Employee" OR "Capitation Fee" OR "Fees, Pharmaceutical" OR "Fees and Charges" OR "Prescription Fees" OR "Single-Payer System") OR (TI:"cost sharing" OR copayment* OR "co payment" OR "co payments" OR coinsurance OR "co insurance" OR deductible* OR "tiered system" OR "tiered systems" OR multitier OR "multi tier" OR onetier OR "one tier" OR "1 tier" OR twotier OR "two tier" OR "2 tier" OR threetier OR "three tier" OR "3 tier" OR "costos compartidos" OR "costos compartir" OR "costos compartido" OR "costos compartiendo" OR deducible* OR coseguro OR "co seguro" OR copag* OR "co pago" OR "sistema de niveles" OR multinivel* OR "multi niveles" OR "un nivel" OR "dos niveles" OR "tres niveles" OR "custo compartilhar" OR "custo compartilhado" OR "custo compartilhando" OR dedutivel* OR dedutiveis OR "co seguro" OR "co seguros" OR coseguro* OR copag* OR "co pago" OR "co pagamento" OR "sistema de niveis" OR multinivel* OR "multi nivel" OR univel* OR binivel* or trinivel*) OR (AB:"cost sharing" OR copayment* OR "co payment" OR "co payments" OR coinsurance OR "co insurance" OR deductible* OR "tiered system" OR "tiered systems" OR multitier OR "multi tier" OR onetier OR "one tier" OR "1 tier" OR twotier OR "two tier" OR "2 tier" OR threetier OR "three tier" OR "3 tier" OR "costos compartidos" OR "costos compartir" OR "costos compartido" OR "costos compartiendo" OR deducible* OR coseguro OR "co seguro" OR copag* OR "co pago" OR "sistema de niveles" OR multinivel* OR "multi niveles" OR "un nivel" OR "dos niveles" OR "tres niveles" OR "custo compartilhar" OR "custo compartilhado" OR "custo compartilhando" OR dedutivel* OR dedutiveis OR "co seguro" OR "co seguros" OR coseguro* OR copag* OR "co pago" OR "co pagamento" OR "sistema de niveis" OR multinivel* OR "multi nivel" OR univel* OR binivel* or trinivel*)) AND ((MH:"Pharmaceutical Preparations" OR "Drug Prescriptions" OR "Drug Utilization" OR "Drug Costs") OR (TI:drug OR drugs OR pharmaceutic* OR medicines OR medication OR drogas OR farmacos OR farmaceutico* OR medicamento* OR medicat* OR droga OR farmacos OR farmaceutico* OR remedios OR medicamentos OR medicat*) OR (AB:drug OR drugs OR pharmaceutic* OR medicines OR medication OR drogas OR farmacos OR farmaceutico* OR medicamento* OR medicat* OR droga OR farmacos OR farmaceutico* OR remedios OR medicamentos OR medicat*)) AND ((PT:"Randomized controlled trial" OR "Controlled clinical trial") OR (MH:Intervention Study OR Evaluation Study OR Comparative Study) OR (TI:randomis* OR randomiz* OR randomly OR intervention* OR control* OR compar* OR evaluat* OR "time series" OR pretest OR posttest OR "pre test" OR "post test" OR impact OR chang* OR effect* OR experiment* OR "ensayo clinico controlado aleatorio" OR "ensayo clinico controlado" OR aleatorios OR intervenc* OR control* OR compar* OR evalua* OR "series de tiempo" OR "pre test" OR "prueba previa" OR "despues de la prueba" OR impacto* OR camb* OR effect* OR experiment*OR "ensaio clinico controlado aleatorio" OR "ensaio clinico controlado" OR intervenc* OR control* OR compare* OR avalia* OR "series temporais" OR "pre teste" OR "pos teste" OR impacto OR mudanc* OR efeit* OR experiment*) OR (AB:randomis* OR randomiz* OR randomly OR intervention* OR control* OR compar* OR evaluat* OR "time series" OR pretest OR posttest OR "pre test" OR "post test" OR impact OR chang* OR effect* OR experiment* OR "ensayo clinico controlado aleatorio" OR "ensayo clinico controlado" OR aleatorios OR intervenc* OR control* OR compar* OR evalua* OR "series de tiempo" OR "pre test" OR "prueba previa" OR "despues de la prueba" OR impacto* OR camb* OR effect* OR experiment*OR "ensaio clinico controlado aleatorio" OR "ensaio clinico controlado" OR intervenc* OR control* OR compare* OR avalia* OR "series temporais" OR "pre teste" OR "pos teste" OR impacto OR mudanc* OR efeit* OR experiment*))

Appendix 11. Search strategy: AIM (AFRO), IMEMR (EMRO), IMSEAR (SEARO) and WPRIM (WPRO) (Global Health Library WHO)

("cost sharing" OR copayment* OR "co payment" OR "co payments" OR coinsurance OR "co insurance" OR deductible* OR "tiered system" OR "tiered systems" OR multitier OR "multi tier" OR onetier OR "one tier" OR "1 tier" OR twotier OR "two tier" OR "2 tier" OR threetier OR "three tier" OR "3 tier") AND (drug OR drugs OR pharmaceutic* OR medicines OR medication) AND (randomis* OR randomiz* OR randomly OR intervention* OR control* OR compar* OR evaluat* OR "time series" OR pretest OR posttest OR "pre test" OR "post test" OR impact OR chang* OR effect* OR experiment*)

Appendix 12. Search strategy: PubMed (not in MEDLINE)

#6 Search #4 NOT #5

#5 Search medline[sb]

#4 Search #1 OR #2 OR #3

#3 Search (prescrip*[tiab] OR prescrib*[tiab]) AND (cap[tiab] OR caps[tiab])

#2 Search prescription charg*[tiab] OR prescription limit*[tiab] OR prescription fee[tiab] OR prescription fees[tiab] OR incentive based formular*[tiab]

#1 Search (capitation*[tiab] OR ceiling[tiab] OR ceilings[tiab] OR coinsur*[tiab] OR co insur*[tiab] OR copay*[tiab] OR co pay*[tiab] OR cost sharing[tiab] OR deductible*[tiab] OR max contribut*[tiab] OR maximum contribut*[tiab] OR consumer charg*[tiab] OR patient charg*[tiab] OR consumer fee[tiab] OR consumer fees[tiab] OR patient fee[tiab] OR patient fees[tiab] OR "out of pocket"[tiab] OR pocket pay*[tiab] OR pocket cost*[tiab] OR tier[tiab] OR tiered system*[tiab] OR onetier*[tiab] OR twotier*[tiab] OR threetier*[tiab] OR multitier*[tiab]) AND (drug[tiab] OR drugs[tiab] OR medicament*[tiab] OR medicat*[tiab] OR medicines[tiab] OR pharmaceutic*[tiab] OR prescrib*[tiab] OR prescrip*[tiab])

Appendix 13. Search strategy: SCOPUS

TITLE-ABS-KEY((({cost sharing}) OR (copayment*) OR ("co payment*") OR (coinsurance) OR ("co insurance") OR (deductible*) OR ({benefit plan}) OR ({benefit plans}) OR ({drug benefit}) OR ({drug benefits}) OR ({user fee}) OR ({user-fee}) OR ({user fees}) OR ({user-fees}) OR ({capitation fee}) OR ({capitation fees}) OR ({out of pocket}) OR ({out-of-pocket}) OR ("cash pay*") OR ("direct pay*") OR ("patient* pay*") OR ("prescri* W/3 cap") OR ("prescri* W/3 caps") OR ({tiered system}) OR ({tiered systems}) OR {multitier} OR {multi tier} OR {multi-tier} OR {onetier} OR {one tier} OR {one-tier} OR {1 tier} OR {1-tier} OR {twotier} OR {two tier} OR {two-tier} OR {2 tier} OR {2-tier} OR {threetier} OR {three tier} OR {three-tier} OR {3 tier} OR {3-tier}) AND (({drug}) OR ({drugs}) OR (pharmaceutic*) OR (medicines) OR (medication)) AND ((randomis*) OR (randomiz*) OR (randomly) OR (intervention*) OR (control*) OR (compar*) OR (evaluat*) OR ({time series}) OR (pretest) OR (posttest) OR ("pre test") OR ("post test") OR (impact) OR (chang*) OR (effect*) OR (experiment*)))

Appendix 14. Search strategy: SciELO (BIREME)

("cost sharing" OR copayment* OR "co payment" OR "co payments" OR coinsurance OR "co insurance" OR deductible* OR "tiered system" OR "tiered systems" OR multitier OR "multi tier" OR onetier OR "one tier" OR "1 tier" OR twotier OR "two tier" OR "2 tier" OR threetier OR "three tier" OR "3 tier" OR "costos compartidos" OR "costos compartir" OR "costos compartido" OR "costos compartiendo" OR deducible* OR coseguro OR "co seguro" OR copag* OR "co pago" OR "sistema de niveles" OR multinivel* OR "multi niveles" OR "un nivel" OR "dos niveles" OR "tres niveles" OR "custo compartilhar" OR "custo compartilhado" OR "custo compartilhando" OR dedutivel* OR dedutiveis OR "co seguro" OR "co seguros" OR coseguro* OR copag* OR "co pago" OR "co pagamento" OR "sistema de niveis" OR multinivel* OR "multi nivel" OR univel* OR binivel* or trinivel*) AND (drug OR drugs OR pharmaceutic* OR medicines OR medication OR drogas OR farmacos OR farmaceutico* OR medicamento* OR medicat* OR droga OR farmacos OR farmaceutico* OR remedios OR medicamentos OR medicat*) AND (randomis* OR randomiz* OR randomly OR intervention* OR control* OR compar* OR evaluat* OR "time series" OR pretest OR posttest OR "pre test" OR "post test" OR impact OR chang* OR effect* OR experiment* OR "ensayo clinico controlado aleatorio" OR "ensayo clinico controlado" OR aleatorios OR intervenc* OR control* OR compar* OR evalua* OR "series de tiempo" OR "pre test" OR "prueba previa" OR "despues de la prueba" OR impacto* OR camb* OR effect* OR experiment*OR "ensaio clinico controlado aleatorio" OR "ensaio clinico controlado" OR intervenc* OR control* OR compare* OR avalia* OR "series temporais" OR "pre teste" OR "pos teste" OR impacto OR mudanc* OR efeit* OR experiment*)

Appendix 15. Search strategy: International Clinical Trials Registry Platform (ICTRP), Word Health Organization (WHO)

coinsurance OR copayment OR co-payment [In the Title]
OR
coinsurance OR copayment OR co-payment [In the Condition]
OR
coinsurance OR copayment OR co-payment [In the Intervention]

Appendix 16. Search strategy: ClinicalTrials.gov, US National Institutes of Health (NIH)

coinsurance OR copayment OR co-payment

Appendix 17. Search strategy: OpenGrey

("cost sharing" OR copayment* OR "co payment" OR "co payments" OR coinsurance OR "co insurance" OR deductible* OR "benefit plan" OR "benefit plans" OR "drug benefit" OR "drug benefits" OR "user fee" OR "user fees" OR capitat* OR fee OR fees OR "out of pocket" OR "cash payment" OR "direct payment" OR "patient payment" OR "single payer" OR "tiered system" OR "tiered systems" OR multitier OR "multi tier" OR onetier OR "one tier" OR "1 tier" OR twotier OR "two tier" OR "2 tier" OR threetier OR "three tier" OR "3 tier") AND (drug OR drugs OR pharmaceutic* OR medicines OR medicament* OR medicat* OR prescri* OR pharmac*)

Appendix 18. Search strategy: JOLIS (three individual searches)

1. cost near shar$ OR copayment$ OR co adj payment OR coinsur$ OR co adj insur$ OR deductible$ OR benefit adj plan$ OR drug adj benefit $ OR user adj fee OR user adj fees OR prescri$ adj fee OR prescri$ adj fees OR capitated OR capitation OR cap OR caps
AND
drug OR drugs OR pharmaceutic$ OR medicines OR medicament$ OR medicat$ OR prescri$ OR pharmac$
2. out adj1 pocket OR cash near pay$ OR direct near pay$ OR patient adj payment$ OR single adj pay$ OR tiered adj system$ OR multitier OR multi adj tier
AND
drug OR drugs OR pharmaceutic$ OR medicines OR medicament$ OR medicat$ OR prescri$ OR pharmac$
3. onetier OR one adj tier OR 1 adj tier OR twotier OR two adj tier OR 2 adj tier OR threetier OR three adj tier OR 3 adj tier
AND
drug OR drugs OR pharmaceutic$ OR medicines OR medicament$ OR medicat$ OR prescri$ OR pharmac$

Appendix 19. Search strategy: OECDiLibrary

drug OR drugs OR pharmaceutic* OR medicament* OR medicines OR prescrip* OR prescrib*] in Title and abstracts, in books, papers and factbooks

Appendix 20. Search strategy: World Bank e-Library

drug OR drugs OR pharmaceutic* OR medicament* OR medicines OR prescrip* OR prescrib*in the fields <Title/subtile> and <Abstract>

Appendix 21. Search strategy: WHO (publications)

drug OR drugs OR pharmaceutic* OR medicament* OR medicines OR prescrip* OR prescrib*, em Title OR TEXT

in the fields <Subjects> and < Commonly used Search terms> the terms Financing and Pricing were marked.

Appendix 22. Search strategy: World Bank Documents & Reports

Topic: Communities and Human Settlements; Finance and Financial Sector Development; Health Nutrition and Population; Privat Sector Development; Public Sector Development; Social Development

Search A: drug benefit

Search B: drug benefits

Search C: co payment

Search D: capitation fee

Search E: capitation fees

Search F: drug insurance

WHAT'S NEW

Date	Event	Description
4 May 2015	New citation required but conclusions have not changed	Seventeen new papers are included in this update. Nine CBA studies included in the previous review are now excluded because they included only 1 site in the intervention or control groups. The total included studies in the review is now 32.
6 October 2013	New search has been performed	This is the first update of the original review. A new search was conducted and the databases searched were expanded to identify studies from low- and middle-income countries. Major changes: New author team conducted this update of the original review.

Date	Event	Description
		New classification for intervention - studies were redistributed in new categories. New classification for medicines - instead of being classified as essential and non-essential (considered as not consistent among studies and confusing with the widespread WHO essential medicines concept), medicines were classified as overall, medicines for symptomatic conditions and medicines for asymptomatic conditions. Each paper is now specifically considered, instead of being grouped as in the original review, with exception of Newhouse 1993, that comprises 5 papers. Bias assessment criteria were updated, and risk of bias tables were added. New summary of findings tables were prepared, and the text was edited to ensure consistency with these.

CONTRIBUTIONS OF AUTHORS

Vera Lucia Luiza co-ordinated the study, screened papers and extracted data; Luisa Arueira Chaves strongly participated in the writing and analysis, screened papers and extracted data; Rondinelli MM Silva, Isabel Cristina M Emmerick and Gabriela Costa Chaves screened papers, extracted data and participated in the analysis. Silvia Cristina Fonseca de Araújo and Elaine L L Moraes screened papers and extracted data; and Andrew D Oxman guided on methods performance.

DECLARATIONS OF INTEREST

No co-author involved has identified any conflict of interest.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- Alliance for Health Policy and Systems Research - Access to Medicines Project, Switzerland.

  Financial support provided

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The title was changed from “Pharmaceutical policies: effects of cap and co-payment on rational drug use” to “ Pharmaceutical policies: effects of cap and co-payment on rational use of medicines” because the word “drug” can be confused with illicit substances.

NOTES

We started from the text of the previous version of this systematic review, and some parts of the text remain unchanged.

INDEX TERMS

Medical Subject Headings (MeSH)

*Cost Sharing; *Drug Costs; *Fees, Pharmaceutical; Drug and Narcotic Control [*economics]; Insurance, Health, Reimbursement [economics]; Pharmaceutical Preparations [*economics]